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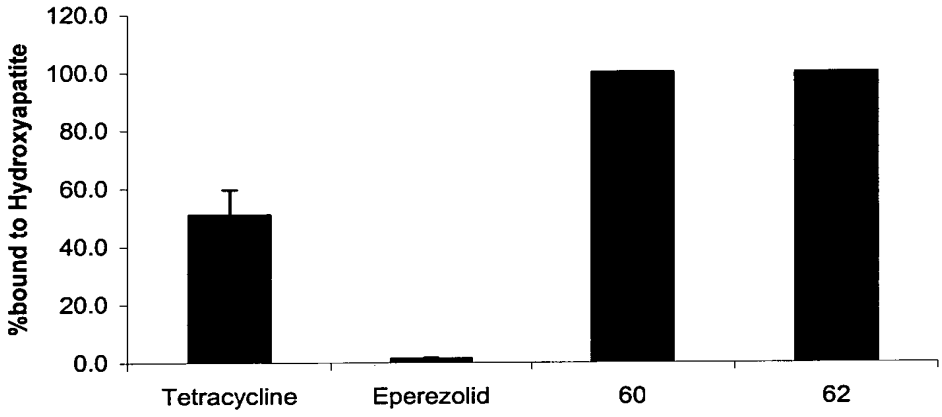
(54) Title: PHOSPHONATED OXAZOLIDINONES AND USES THEREOF FOR THE PREVENTION AND TREATMENT OF BONE AND JOINT INFECTIONS



(57) Abstract: The invention relates to phosphonated derivatives of oxazolidinones. These compounds are useful as antibiotics for prevention and/or the treatment of bone and joint infections, especially for the prophylaxis and/or treatment of osteomyelitis.

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PHOSPHONATED OXAZOLIDINONES AND USES THEREOF FOR THE PREVENTION AND TREATMENT OF BONE AND JOINT INFECTIONS

BACKGROUND OF THE INVENTION

a) Field of the invention

The invention relates to phosphonated derivatives of oxazolidinones. These compounds are useful as antibiotics for prevention and/or the treatment of bone and joint infections, especially for the prophylaxis and/or treatment of osteomyelitis.

b) Brief description of the prior art

Osteomyelitis is an inflammation of bone caused by a variety of microorganisms, mainly *Staphylococcus aureus* (Carek *et al.*, American Family Physician (2001), Vol 12, 12:2413-2420). This painful and debilitating disease occurs more commonly in children. Within the adult population, diabetics and kidney dialysis patients are also vulnerable. The acute form of the disease is treatable with antibiotics, but requires a lengthy period of daily therapy. It can, however, revert to a recurrent or chronic form requiring repeated hospital stays and heavy treatment regimens.

Oxazolidinones are a new class of synthetic antimicrobial agents which inhibit the initiation of protein synthesis at the ribosomal level (Renslo *et al* Bioorganic & Medicinal Chemistry (2006), 14, 4227-4240). Best known oxazolidinones are certainly linezolid (International PCT patent application WO 95/07271) and eperezolid (US patent No. 5,652,238). Both drugs were proven clinically and microbiologically to have potent activity against gram-positive organisms including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp., and *Streptococcus* spp. Although the use of highly active oral anti-staphylococcal agents for the treatment of bone and joint infections is becoming attractive, results obtained in a rat model using linezolid for the treatment of osteomyelitis have not been convincing (Patel *et al.* Antimicrobial agents and Chemotherapy (2000) Vol 44, 12:3438-40). The problem may be that, although linezolid demonstrates a good penetration in a variety of tissues, including bone (Lovering *et al.*, Journal of Antimicrobial Chemotherapy (2002), 50:73-77) and osteo-articular tissues (Rana *et al.*, Journal of Antimicrobial Chemotherapy (2002), 50:747-750), the actual intra-bone concentration of the drug remains low (Kutscha-Lissberg *et al.*, Antimicrobial agents and Chemotherapy (2003), 47: 3964-66). Therefore, linezolid could prove to be more effective if its intra-bone concentration could be increased.

Bisphosphonates are well-characterized bone-seeking agents. These compounds are known to have a high affinity to the bones due to their ability to bind the Ca^{2+} ions found in the

hydroxyapatite forming the bone tissues (Hirabayashi and Fujisaki, Clin. Pharmacokinet. (2003) 42(15): 1319-1330). Therefore, many different types of bisphosphonate-conjugated compounds have been made for targeting drugs selectively to the bone, including proteins (Uludag *et al.*, Biotechnol Prog. (2000) 16:1115-1118), vitamins (US 6,214,812 and WO 02/083150), tyrosine kinase inhibitors (WO 01/44258 and WO 01/44259), hormones (US 5,183,815) and bone scanning agents (US 4,810,486). These and other bisphosphonate derivatives have been used as therapeutic agents for bone diseases such as arthritis (US 4,746,654), osteoporosis (US 5,428,181 and US 6,420,384), hypercalcemia (US 4,973,576), and bone cancers (US 6,548,042). Although some have suggested that bisphosphonate-antibiotics could also be made, only few of such compounds have actually being synthesized, including macrolides (US 5,359,060), fluoroquinolones and β-lactams (US 5,854,227; US 5,880,111; DE 195 32 235; Pieper and Keppler, Phosphorus, Sulfur and Silicon (2001) 170:5-14; and Herczegh *et al.* J. Med. Chem (2002) 45:2338-41). Furthermore, prior to the present invention, no one has ever made or suggested to make phosphonated derivatives of oxazolidinones, nor suggested the use of such derivatives for the prevention or treatment of osteomyelitis.

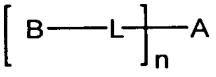
In view of the above, there is a need for highly active antibiotics for the prevention and treatment of bone and joint infections. More particularly, there is a need for oxazolidinones with a higher affinity for bone, and a need for treatment methods wherein the intra-bone concentration of oxazolidinones is increased, for an extended period of time, above the minimal effective inhibitory concentrations which are required for killing bacteria.

The present invention fulfills these needs and also other needs as will be apparent to those skilled in the art upon reading the following specification.

SUMMARY OF THE INVENTION

The present invention is directed to antimicrobial compounds which have an affinity for binding bones. More particularly, the invention is directed to phosphonated derivatives of oxazolidinones. These compounds are useful as antibiotics for the prevention or treatment of bone and joint infections, especially for the prevention and treatment of osteomyelitis.

In one embodiment, the compounds of the invention are represented by the general **Formula (I)** as illustrated below:



(I)

as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

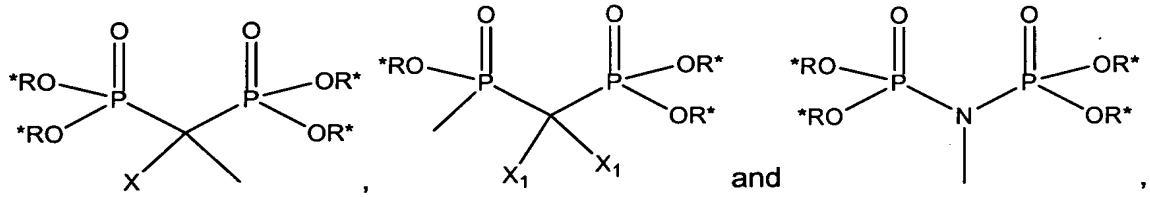
A is an oxazolidinone antimicrobial molecule;

B is a phosphonated group having a high affinity to osseous tissues;

L is a bond or a linker for covalently coupling B to A; and

n is an 1,2 or 3.

In a prefered embodiment, **B** is a phosphonated group having a high affinity to osseous tissues. Preferably **B** is a bisphosphonate. More preferably, **B** is a bisphosphonate selected from the group consisting of:



wherein:

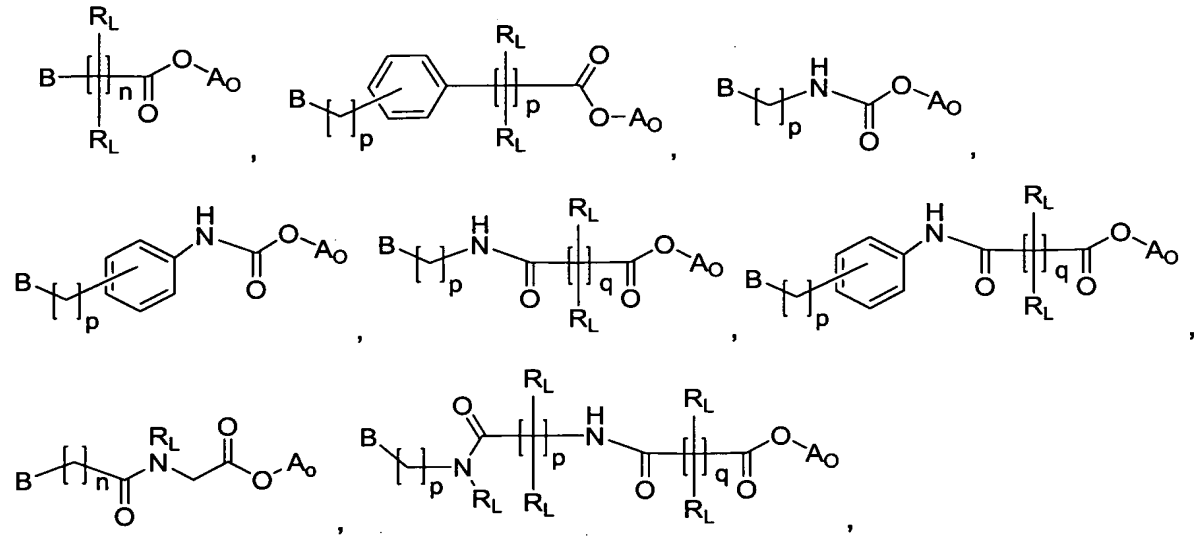
each **R*** is independently selected from the group consisting of H, lower alkyl, cycloalkyl, aryl and heteroaryl, with the proviso that at least two **R*** are H;

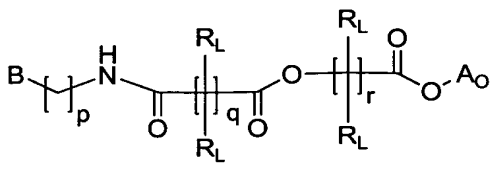
X is H, OH, NH_2, or a halo group; and

$\mathbf{X_1}$ are both H, or each is independently selected from the group consisting of H, OH, NH_2, and a halo group.

In another prefered embodiment, **L** is a cleavable linker for covaltently and reversibly coupling **B** to **A**.

Preferably, **L** couples **B** to **A** through one or more hydroxyl groups on **A**, through one or more nitrogen atoms on **A**, or through one or more hydroxyl groups and one or more nitrogen atoms on **A**. When **L** couples **B** to **A** through a hydroxyl group on **A**, preferably **L** is one of the following linkers:

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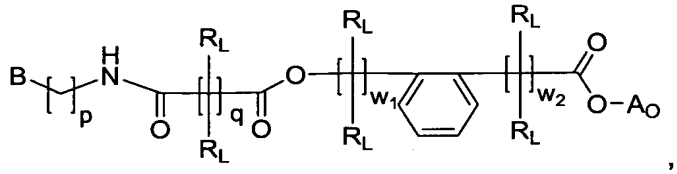
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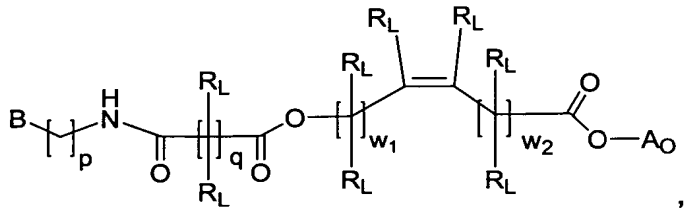
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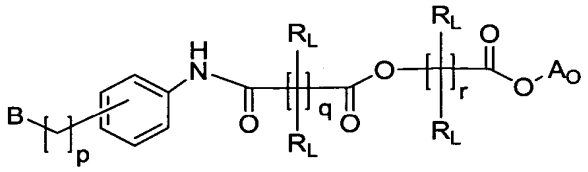
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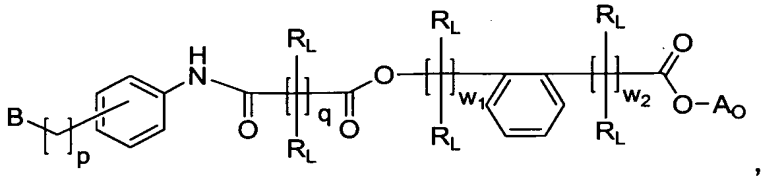
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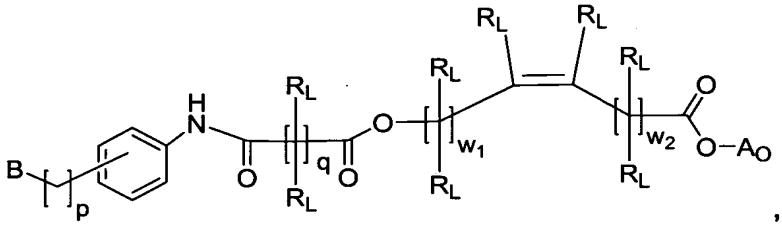
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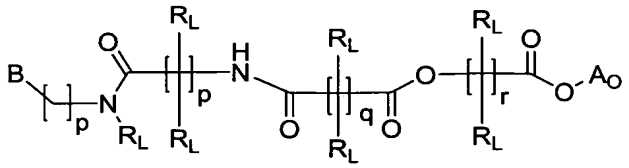
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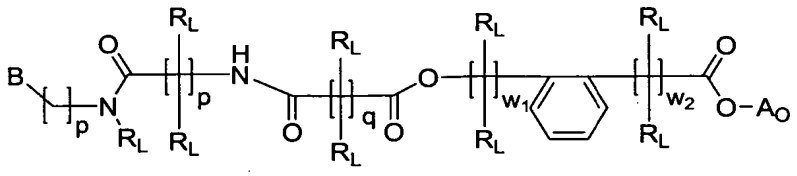
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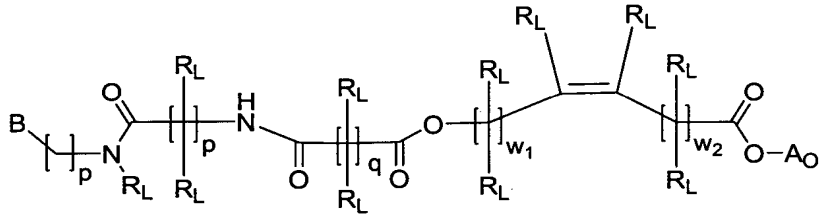


wherein:

n is an integer ≤ 10, preferably 1, 2, 3 or 4, more preferably 1 or 2;

each **p** is independently 0 or an integer ≤ 10, preferably 0, 1, 2, 3 or 4, more preferably 0 or 1;

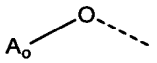
q is 2 or 3

r is 1, 2, 3, 4 or 5

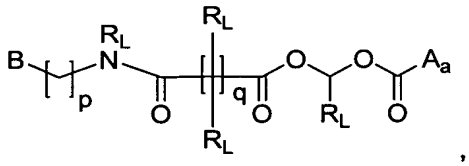
$\mathbf{w_1}$ and $\mathbf{w_2}$ are integers ≥ 0 such that their sum ($\mathbf{w_1} + \mathbf{w_2}$) is 1,2 or 3

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl, preferably H;

B represents the phosphonated group;

and the substructure  of the linker represents the hydroxyl moiety of **A**.

When **L** couples **B** to **A** through a nitrogen atom on **A**, preferably **L** is one of the following linkers: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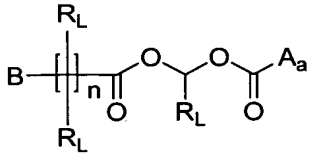
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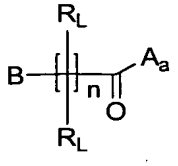
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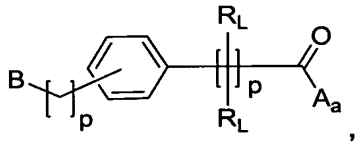
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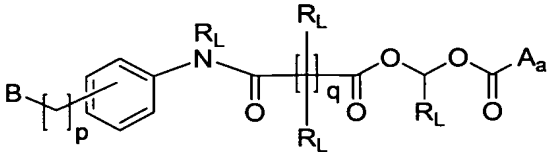
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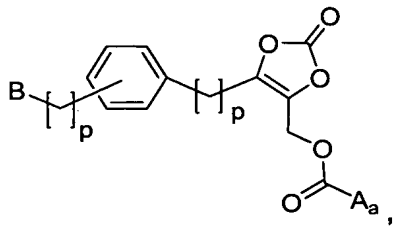
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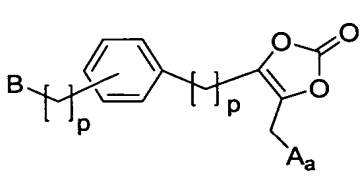
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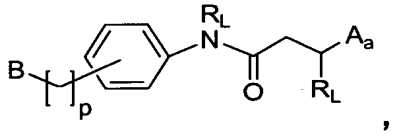
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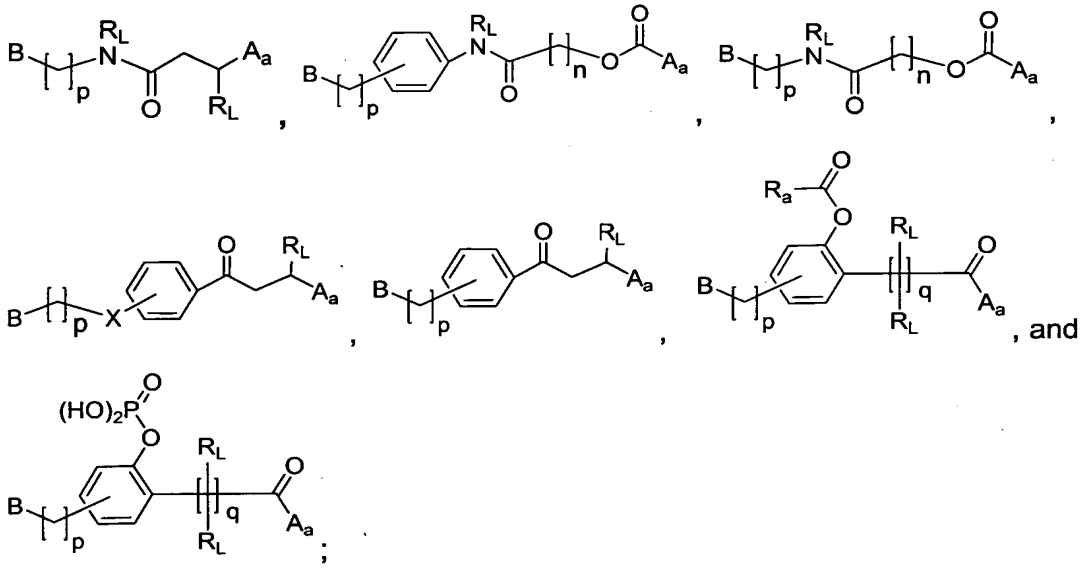


wherein:

n is an integer ≤ 10, preferably 1, 2, 3 or 4, more preferably 1 or 2;

each **p** is independently 0 or an integer ≤ 10, preferably 0, 1, 2, 3 or 4, more preferably 0 or 1;

q is 2 or 3;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl, preferably H;

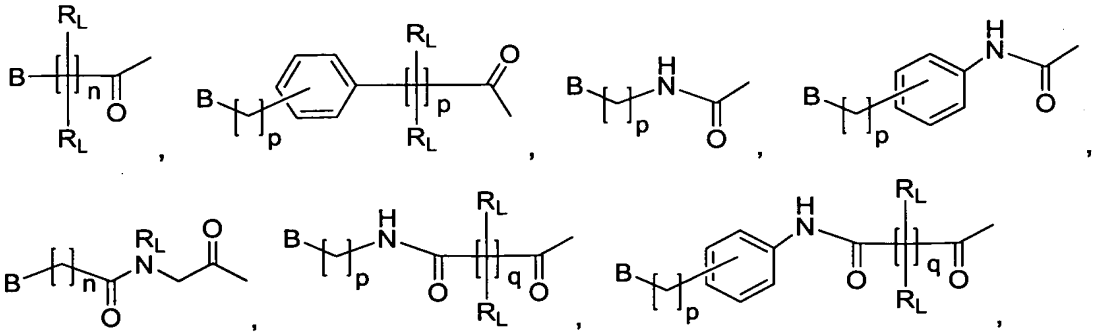
$\mathbf{R_a}$ is C_xH_y where x is an integer of 0 to 20 and y is an integer of 1 to 2x+1;

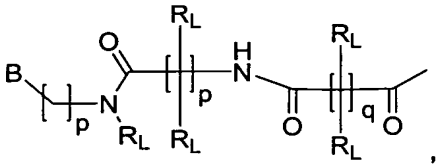
X is CH_2, —CON$\mathbf{R_L}$—, —CO—O—CH_2—, or —CO—O—;

B represents the phosphonated group; and

$\mathbf{A_a}$ represents the nitrogen atom on **A**.

In further prefered embodiment, at least one of **B—L—** is coupled to a hydroxyl functionality on the oxazolidinone antimicrobial molecule **A**. Preferably, when **B—L—** is coupled to a hydroxyl functionality **B—L—** is one of the following:

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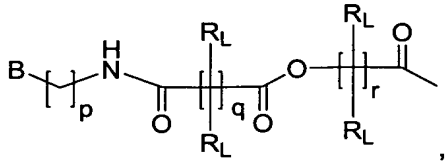
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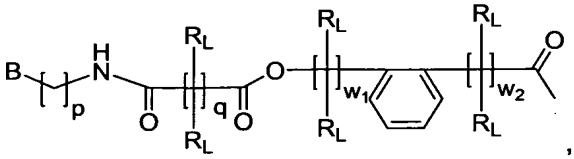
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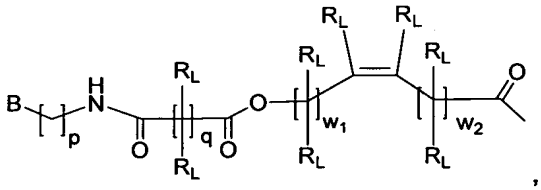
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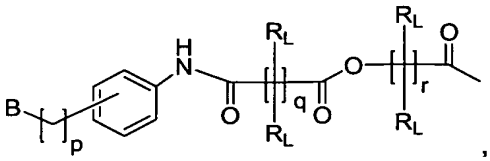
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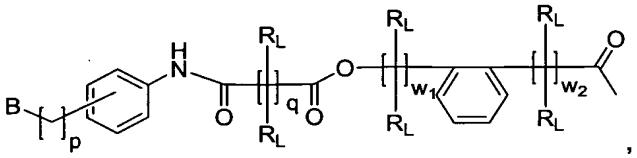
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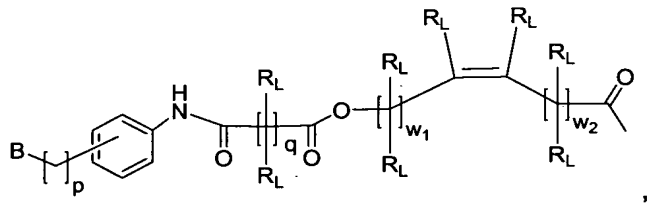
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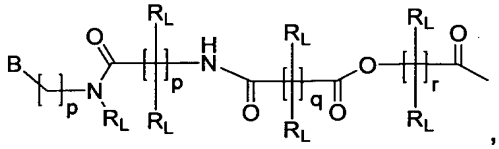
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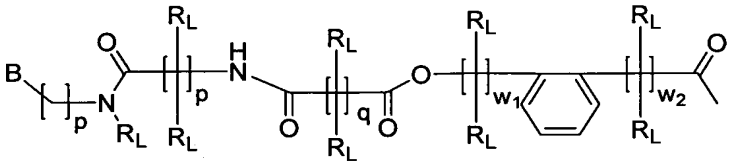
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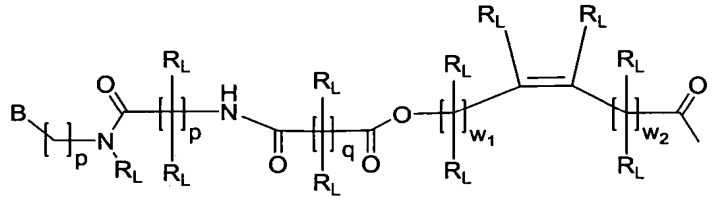


wherein:

B represents a phosphonated group;

each **p** is independently 0 or an integer ≤ 10, preferably 0, 1, 2, 3, or 4, more preferably 0 or 1;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl, preferably H;

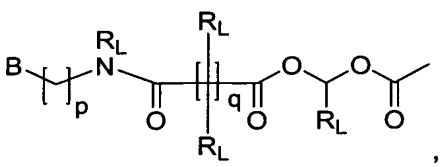
q is 2 or 3;

n is an integer ≤ 10, preferably 1, 2, 3, or 4, more preferably 1 or 2;

r is 1, 2, 3, 4 or 5; and

$\mathbf{w_1}$ and $\mathbf{w_2}$ are each integers ≥ 0 such that their sum $(\mathbf{w_1} + \mathbf{w_2})$ is 1, 2 or 3.

In further prefered embodiment, at least one of **B—L—** is coupled to a nitrogen atom on the oxazolidinone antimicrobial molecule **A**. Preferably, when **B—L—** is coupled to a nitrogen atom **B—L—** is one of the following: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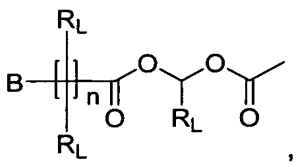
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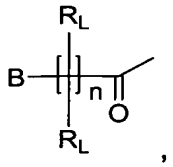
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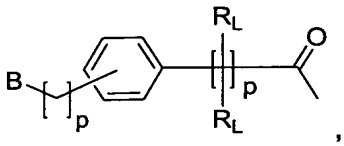
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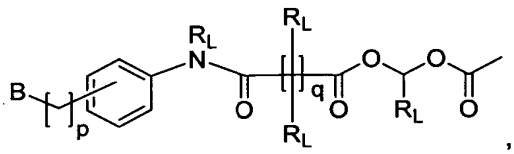
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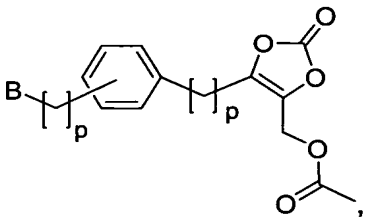
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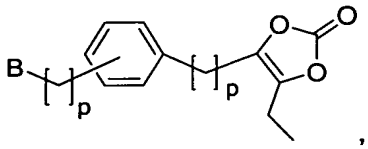
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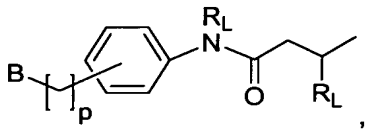
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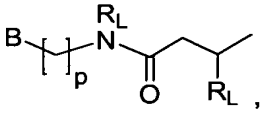
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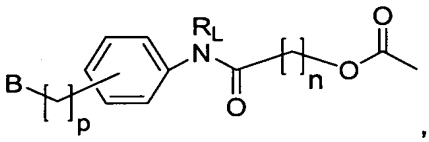
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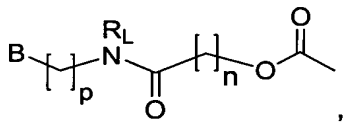
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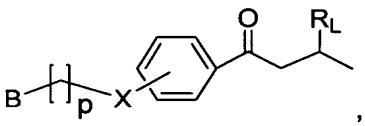
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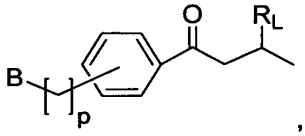
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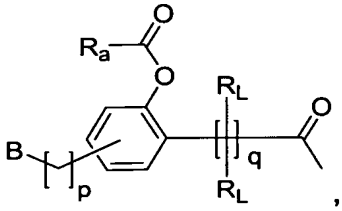
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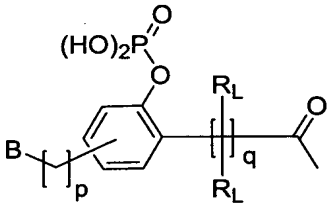


wherein:

B represents said phosphonated group;

n is an integer ≤ 10, preferably 1, 2, 3, or 4, more preferably 1 or 2;

each **p** is independently 0 or an integer ≤ 10, preferably 0, 1, 2, 3, or 4, more preferably 0 or 1;

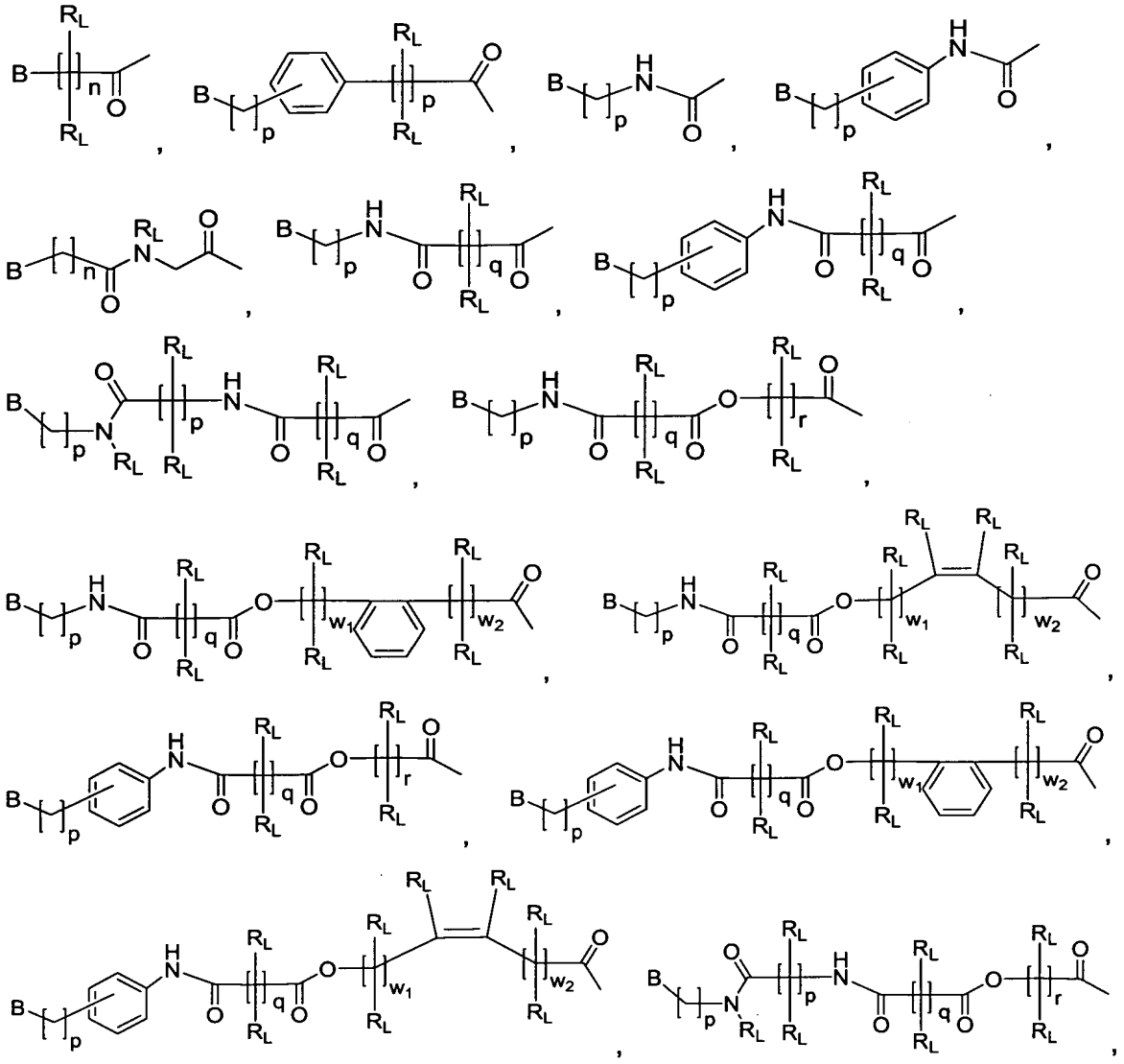
each R_L is independently selected from the group consisting of H, ethyl and methyl, preferably H;

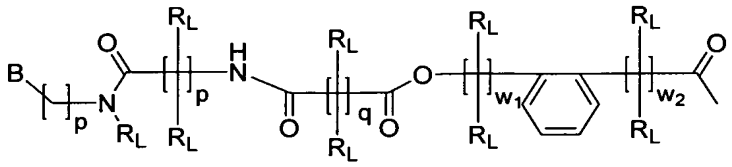
q is 2 or 3;

X is CH_2, —CONR_L—, —CO—O—CH_2—, or —CO—O—; and

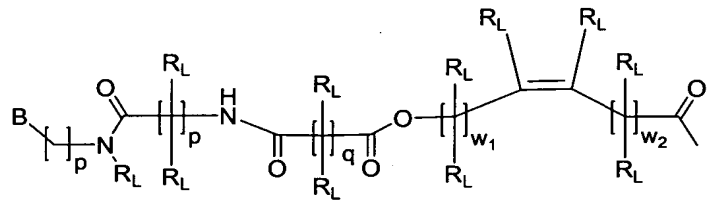
R_a is C_xH_y where x is an integer of 0 to 20 and y is an integer of 1 to 2x+1.

In an additional prefered embodiment, **n** is an integer of 2 to 3, at least one of **B—L—** is coupled to a hydroxyl functionality on the oxazolidinone antimicrobial molecule **A**, and at least one of **B—L—** is coupled to a nitrogen atom on the oxazolidinone antimicrobial molecule **A**. Preferably, when **B—L—** is coupled to a hydroxyl functionality **B—L—** is one of the following:





and



wherein:

B represents a phosphonated group;

each **p** is independently 0 or an integer ≤ 10, preferably 0, 1, 2, 3, or 4, more preferably 0 or 1;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl, preferably H;

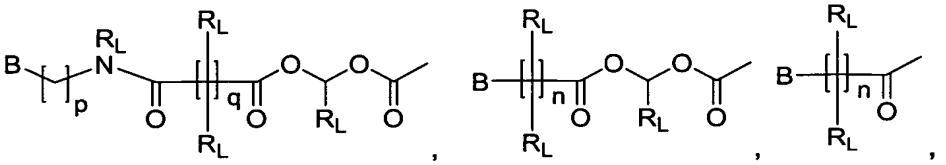
q is 2 or 3;

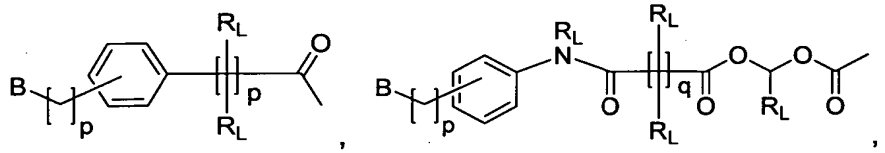
n is an integer ≤ 10, preferably 1, 2, 3, or 4, more preferably 1 or 2;

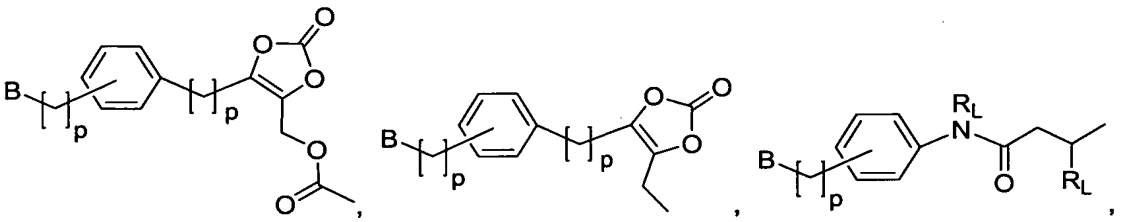
r is 1, 2, 3, 4 or 5; and

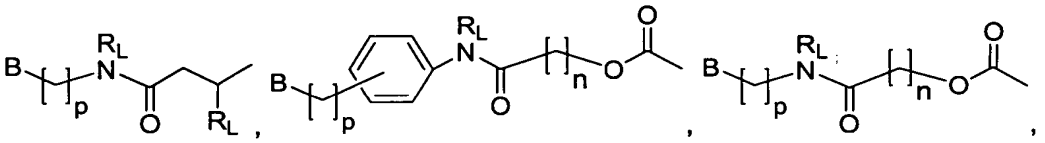
$\mathbf{w_1}$ and $\mathbf{w_2}$ are each integers ≥ 0 such that their sum $(\mathbf{w_1} + \mathbf{w_2})$ is 1, 2 or 3.

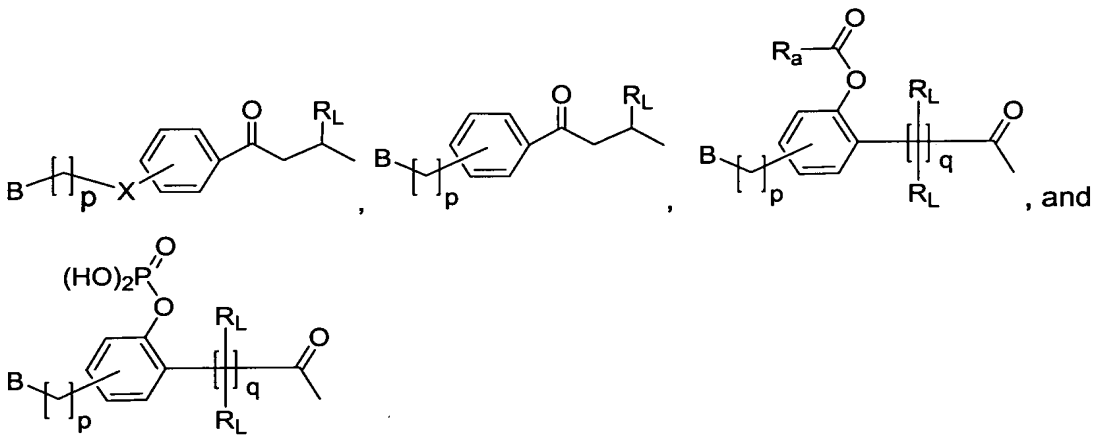
Preferably, when **B—L—** is coupled to a nitrogen atom **B—L—** is one of the following:











wherein:

B represents said phosphonated group;

n is an integer ≤ 10, preferably 1, 2, 3, or 4, more preferably 1 or 2;

each **p** is independently 0 or an integer ≤ 10, preferably 0, 1, 2, 3, or 4, more preferably 0 or 1;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl, preferably H;

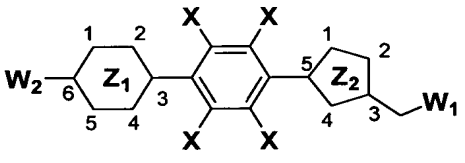
q is 2 or 3;

X is CH_2, —CON$\mathbf{R_L}$—, —CO—O—CH_2—, or —CO—O—; and

$\mathbf{R_a}$ is C_xH_y where x is an integer of 0 to 20 and y is an integer of 1 to 2x+1.

In a further preferred embodiment, **n** is 1, 2 or 3.

Preferably, the oxazolidinone antimicrobial molecule **A** has a structure represented by the following Formula **A1**:

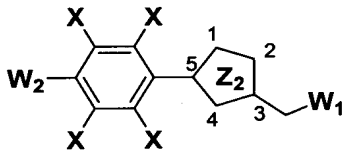


(A_1)

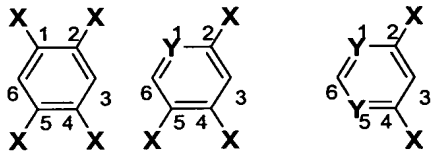
as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

Each of **X** is independently hydrogen or a halogen, preferably a hydrogen or fluorine;

is either absent, in which case A_1 becomes



or is selected from the group consisting of formulae **M1-M3**

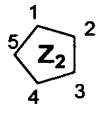


M1 , **M2** and **M3**

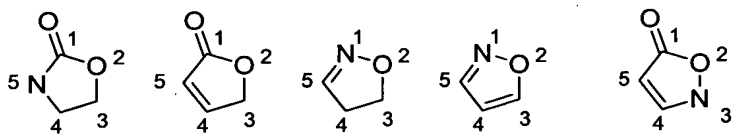
Wherein:

each **X** is defined as above;

each **Y** is independently N or CH



is selected from the group consisting of formulae **M4-M8**

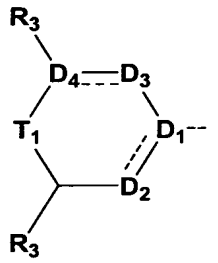
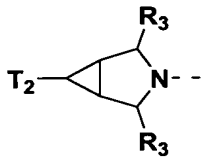


M4 , **M5** , **M6** , **M7** and **M8**

W_1 is hydroxy, halo, amino, azido, (1-4C)alkanesulfonyloxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, $NHS(O)_m$(1-4C)alkyl, $NHCOR_c$, $NHCSR_c$; isoxazol-3-oxy, isothiazol-3-oxy, (1,2,5-thiadiazol)-3-oxy, (1,2,5-oxadiazol)-3-oxy, isoxazol-3-amino, isothiazol-3- amino, (1,2,5-thiadiazol)-3- amino, (1,2,5-oxadiazol)-3-amino, tetrazol-2-yl, tetrazol-1-yl, (1,2,3-triazol)-1-yl, or (4-ethynyl-1,2,3-triazol)-1-yl

wherein: **m** is 0, 1, or 2 and **R_c** is H, (1-4C)alkyl, (1-4C)dihaloalkyl, (1-4C)alkoxy, methoxymethyl, acetylmethyl, methylamino or dimethylamino;

W_2 is selected from the group consisting of formulae **M9-M16**


M9 ,

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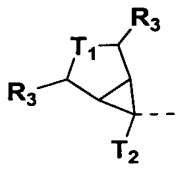
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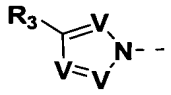
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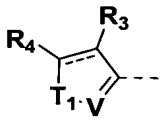
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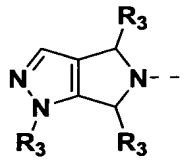
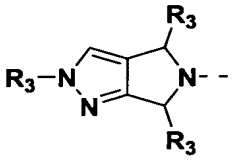
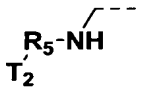

M14 ,

M15 and

M16

D_1, is independently CH or N and D_2, D_3 and D_4, are each independently CH, CH_2, N, S or O and each ----- represents either a single bond or a double bond;

R_3 are each independently H, CH_3, CN, hydroxyl, bromo, oxo (=O), (1-4C)alkyl, (1-4C)alkylamino, (1-4C)alkoxycarbonyl or CO_2R_d, wherein R_d is H, (1-5C)alkyl, phenyl, or heteroaryl;

T_1 is O, S, SO, SO_2, NH, NR_a, $NCOCH_2OH$, or $NCOR_a$, $C(OH)CH_2N(R_a)_2$, $C(OH)CH_2OR_a$, CH-(tetrazol-2-yl), or CH(tetrazol-1-yl)

wherein each R_a is independently H, aryl, (1-4C)alkyl, cycloalkyl, heteroaryl, amino, (1-4C)alkylamino, or OR_b, wherein R_b is (1-6C)alkyl

T_2 is hydroxyl, amino, chloro, fluoro, bromo, $-CO_2H$, cyano, or $-C(O)N(R_d)_2$, wherein each R_d is defined as above.

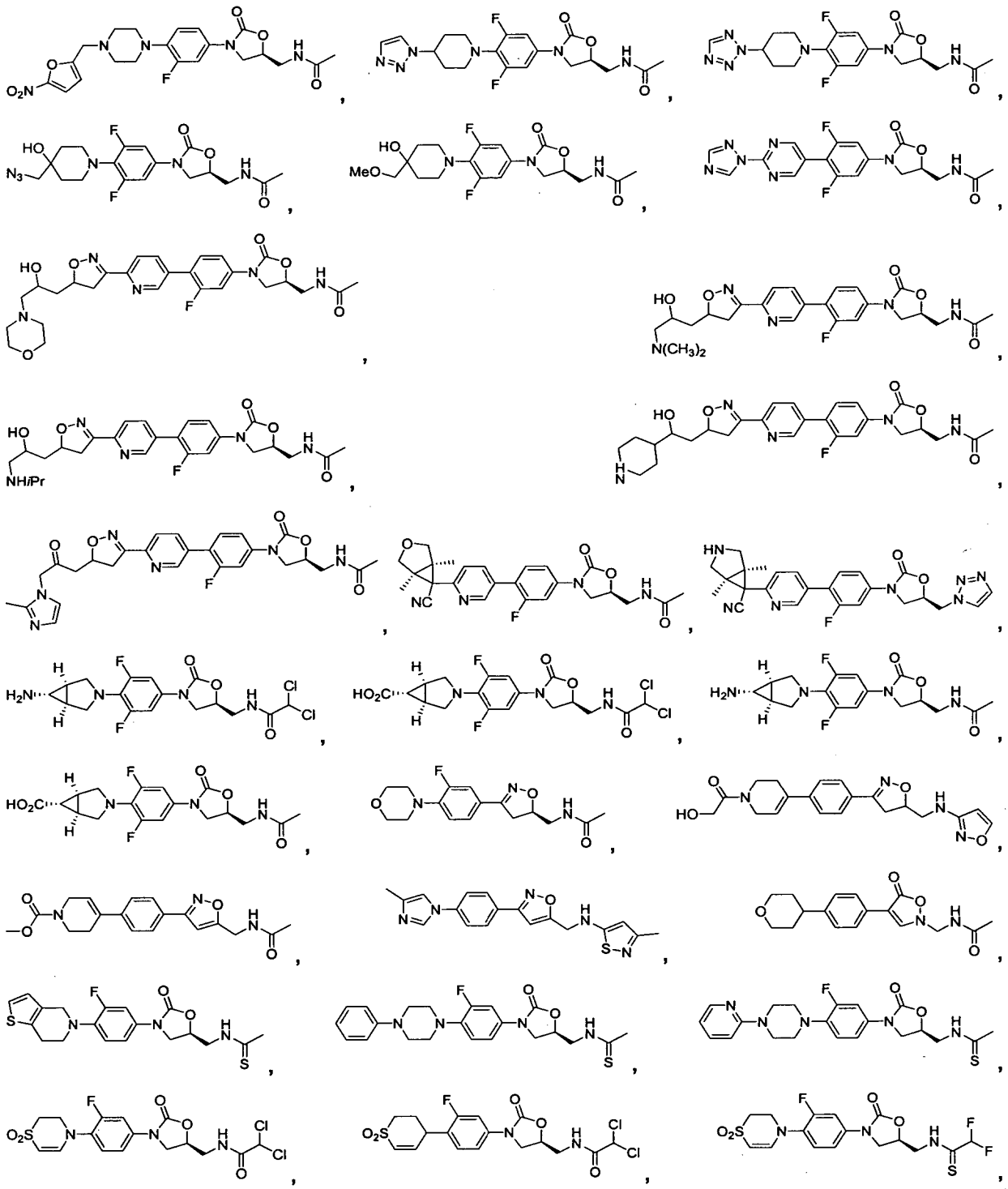
V is N or CH

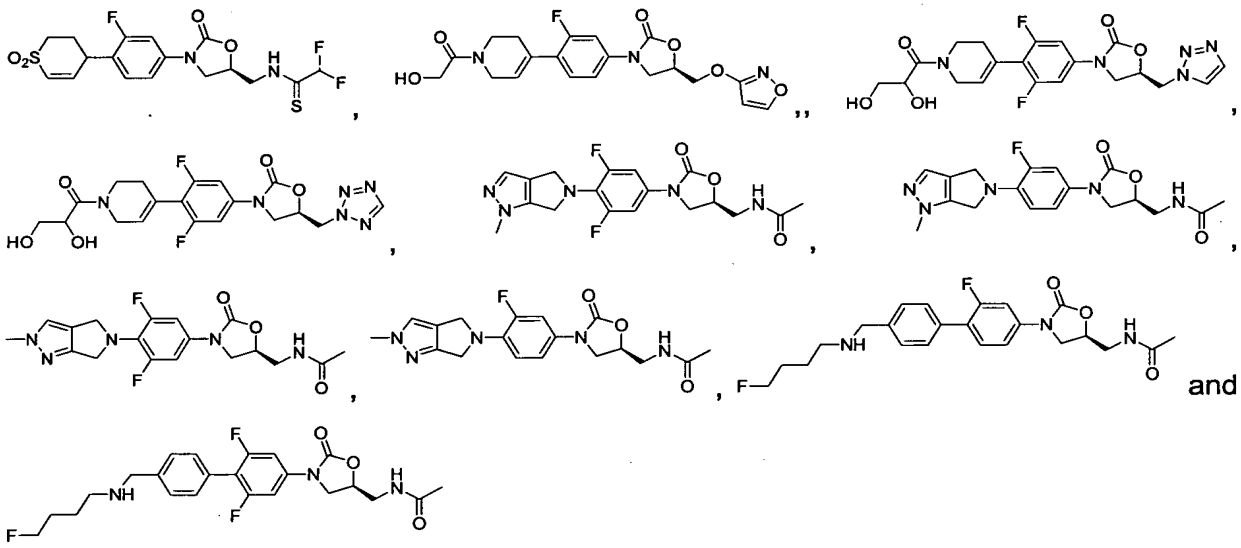
R_4 is H or (1-4C) alkyl, $-(CH_2)_x-(CH(OH))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NH_2))-(CH_2)_y-Q$ or $-(CH_2)_x-C(O)-(CH_2)_y-Q$, wherein x and y are independently 0,1 or 2 and Q is $N(R_d)_2$, imidazol-1-yl, 2-methyl-imidazol-1-yl, tetrazol-2-yl, or (1,2,3-triazol)-1-yl, with R_d defined as above.

R_5 is one of either $-C_aH_b$, $-(CH_2)_a-(CH(OH))-(CH_2)_c-$, $-(CH_2)_a-(CH(NH_2))-(CH_2)_c-$, $-(CH_2)_a-(CH(OH))-(CH_2)_c-C(O)-$, or $-(CH_2)_a-(CH(NH_2))-(CH_2)_c-C(O)-$, wherein a is an integer ≥ 0 and ≤ 10, b is an integer and ≥ 0 and $\leq 2a$ and c is 0,1 or 2.

More preferably, the oxazolidinone antimicrobial molecule **A** is Linezolid, Eperezolid, N-((3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (eperezolid amine)

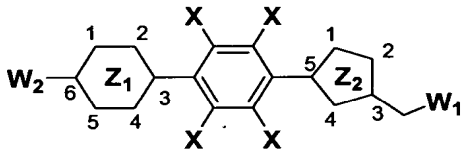
or has a structure represented by one of the following formulas or an antimicrobial derivative thereof:





and

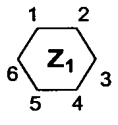
In another embodiment, the compounds of the invention are represented by Formula (II) or a pharmaceutically acceptable salt or prodrug thereof:



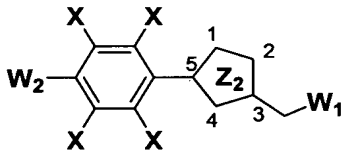
(II)

as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

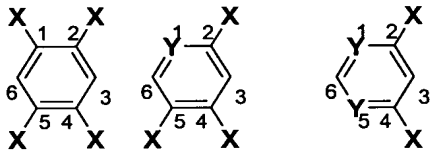
Each of **X** is independently hydrogen or a halogen, preferably a hydrogen or fluorine;



is either absent, in which case II becomes



or is selected from the group consisting of formulae **M1-M3**

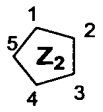


M1 , **M2** and **M3**

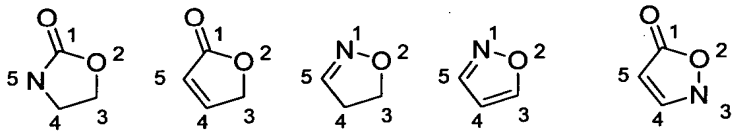
Wherein:

each **X** is defined as above;

each **Y** is independently N or CH



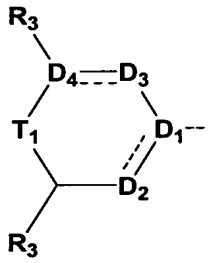
is selected from the group consisting of formulae **M4-M8**



M4 , **M5** , **M6** , **M7** and **M8**

W_1 is hydroxy, halo, amino, azido, (1-4C)alkanesulfonyloxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, $NHS(O)_m$(1-4C)alkyl, $NHCOR_c$ or $NHCSR_c$; isoxazol-3-oxy, isothiazol-3-oxy, (1,2,5-thiadiazol)-3-oxy, (1,2,5-oxadiazol)-3-oxy, isoxazol-3-amino, isothiazol-3- amino, (1,2,5-thiadiazol)-3- amino, (1,2,5-oxadiazol)-3-amino, tetrazol-2-yl, tetrazol-1-yl, (1,2,3-triazol)-1-yl, (4-ethynyl-1,2,3-triazol)-1-yl, $-OL_1$, or $-N(R_c)L_2$ wherein: **m** is 0, 1, or 2; and R_c is H, (1-4C)alkyl, (1-4C)dihaloalkyl, (1-4C)alkoxy, methoxymethyl, acetylmethyl, methylamino or dimethylamino;

W_2 is selected from the group consisting of formulae **M9-M16**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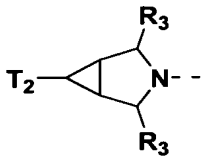
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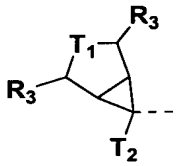
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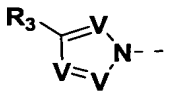
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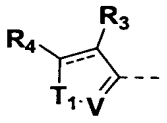
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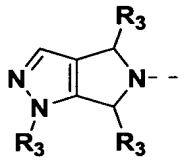
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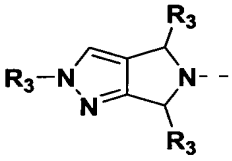
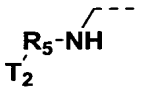

M15 and

M16

D_1, is independently CH or N and D_2, D_3 and D_4, are each independently CH, CH_2, N, S or O and each ----- represents either a single bond or a double bond;

R_3 are each independently H, CH_3, CN, hydroxyl, bromo, oxo (=O), (1-4C)alkyl, (1-4C)alkylamino, (1-4C)alkoxycarbonyl, CO_2R_d, or $-OL_3$ wherein R_d is H, (1-5C)alkyl, phenyl, or heteroaryl;

T_1 is O, S, SO, SO_2, NH, NR_a, $NCOCH_2OH$, $NCOR_a$, $C(OH)CH_2N(R_a)_2$, $C(OH)CH_2OR_a$, CH-(tetrazol-2-yl), CH(tetrazol-1-yl), NL_4, $CHOL_5$, $C(OL_6)CH_2N(R_a)_2$, $C(OH)CH_2N(R_a)L_7$, $C(OL_8)CH_2OR_a$, or $C(OH)CH_2OL_9$

wherein each R_a is independently H, aryl, (1-4C)alkyl, cycloalkyl, heteroaryl, amino, (1-4C)alkylamino, or OR_b, wherein R_b is (1-6C)alkyl

T_2 is hydroxyl, amino, chloro, fluoro, bromo, $-CO_2H$, cyano, $-C(O)N(R_d)_2$, $-OL_{10}$, $-N(R_d)L_{11}$, $-N(L_{12})_2$, $-C(O)N(L_{13})_2$ or $-C(O)N(R_d)(L_{14})$ wherein each R_d is defined as above.

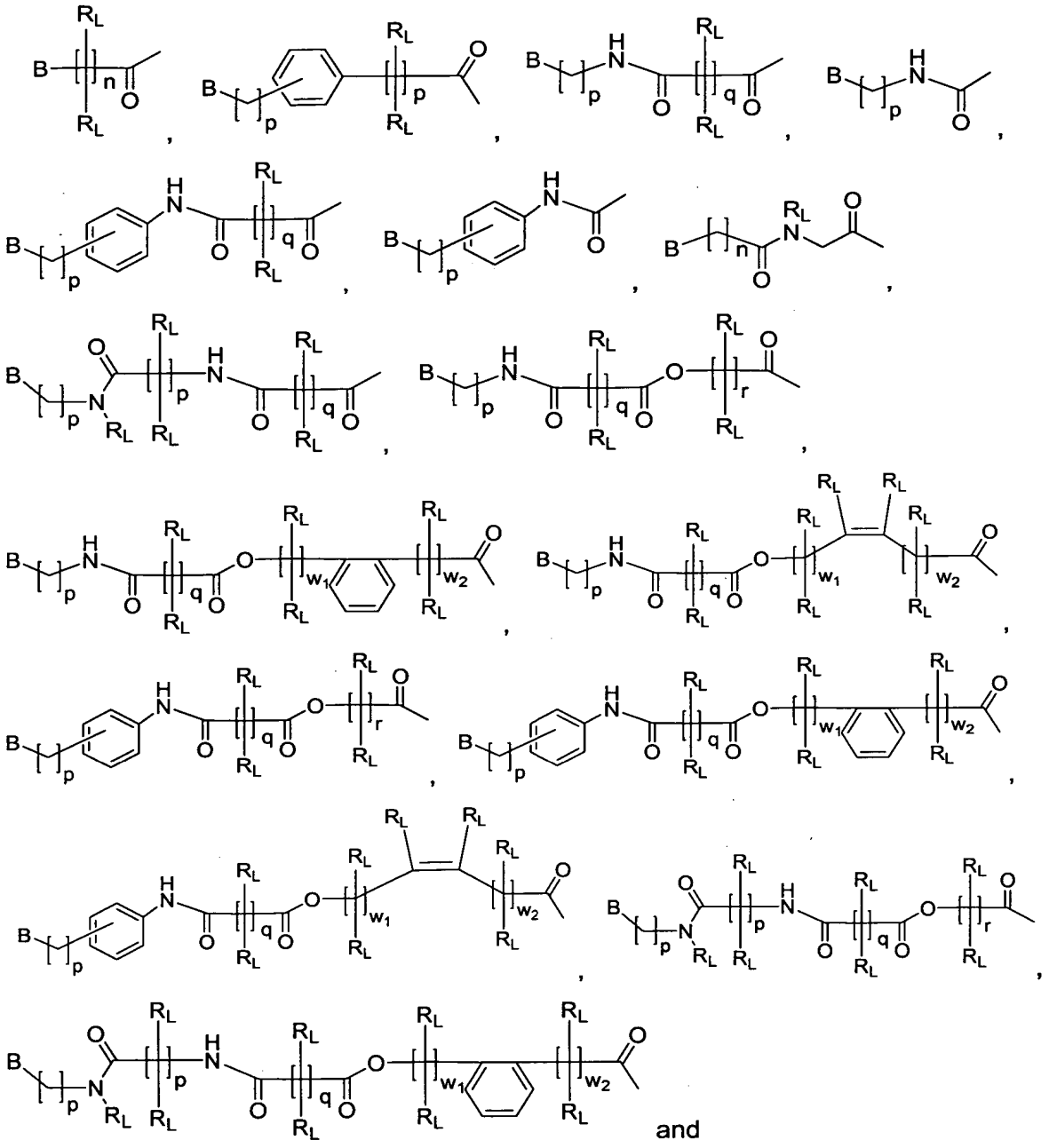
V is N or CH

R_4 is H or (1-4C) alkyl, $-(CH_2)_x-(CH(OH))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NH_2))-(CH_2)_y-Q$, , $-(CH_2)_x-(CH(OL_{15}))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NHL_{16}))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(N(L_{17})_2))-(CH_2)_y-Q$ or $-(CH_2)_x-C(O)-(CH_2)_y-Q$, wherein x and y are independently 0,1 or 2 and Q is $N(R_d)_2$, $N(R_d)L_{18}$, $N(L_{19})_2$ imidazol-1-yl, 2-methyl-imidazol-1-yl, tetrazol-2-yl or (1,2,3-triazol)-1-yl, with R_d defined as above.

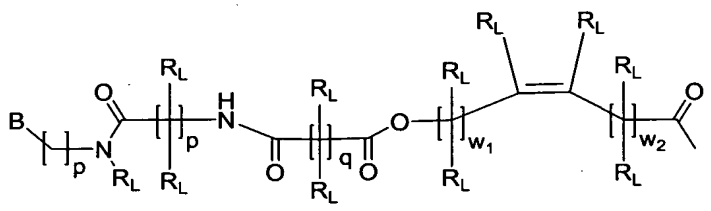
R_5 is one of either $-C_mH_n$, $-(CH_2)_m-(CH(OH))-(CH_2)_b-$, $-(CH_2)_m-(CH(NH_2))-(CH_2)_b-$, $-(CH_2)_m-(CH(OH))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(NH_2))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(OL_{20}))-(CH_2)_b-$, $-(CH_2)_m-(CH(NHL_{21}))-(CH_2)_b-$, $-(CH_2)_m-(CH(N(L_{22})_2))-(CH_2)_b-$, $-(CH_2)_m-(CH(OL_{23}))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(NHL_{24}))-(CH_2)_b-C(O)-$, or $-(CH_2)_m-$

$(CH(N(L_{25})_2))$-$(CH_2)_b$-C(O)-, wherein m is an integer ≥0 and ≤10, n is an integer and ≥0 and ≤2m and b is 0,1 or 2.

Each L_1, L_3, L_5, L_6, L_8, L_9, L_{10}, L_{15}, L_{20}, and L_{23} is a linker independently selected from the group of



and



wherein:

B represents said phosphonated group;

each **p** is independently 0 or an integer ≤ 10;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl;

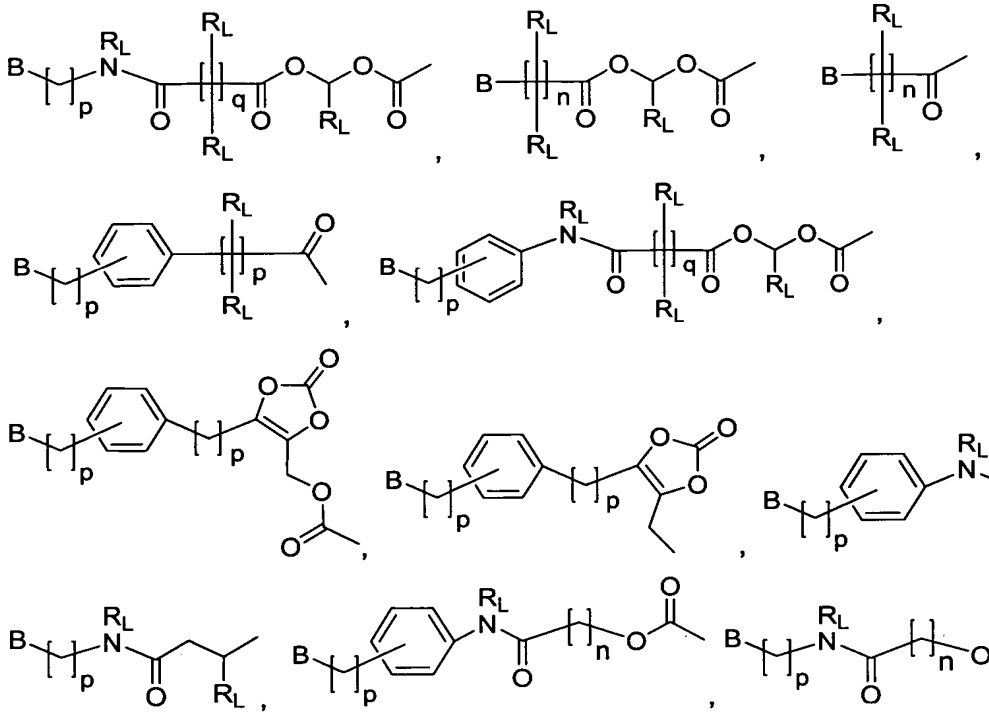
q is 2 or 3;

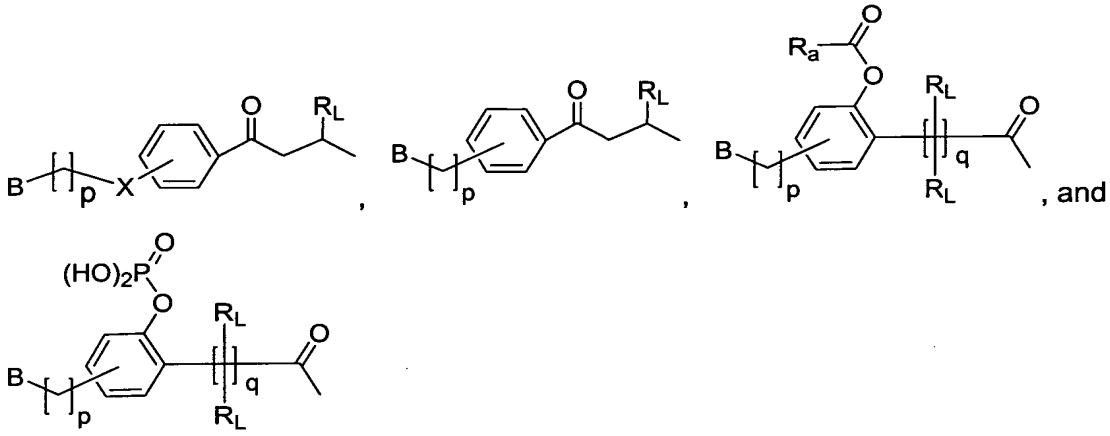
n is an integer ≤ 10;

r is 1, 2, 3, 4 or 5; and

$\mathbf{w_1}$ and $\mathbf{w_2}$ are each integers ≥ 0 such that their sum ($\mathbf{w_1} + \mathbf{w_2}$) is 1, 2 or 3.

Each $\mathbf{L_2}$, $\mathbf{L_4}$, $\mathbf{L_7}$, $\mathbf{L_{11}}$, $\mathbf{L_{12}}$, $\mathbf{L_{13}}$, $\mathbf{L_{14}}$, $\mathbf{L_{16}}$, $\mathbf{L_{17}}$, $\mathbf{L_{18}}$, $\mathbf{L_{19}}$, $\mathbf{L_{21}}$, $\mathbf{L_{22}}$, $\mathbf{L_{24}}$, and $\mathbf{L_{25}}$ is a linker independently selected from the group of





wherein:

B represents said phosphonated group;

n is an integer ≤ 10;

each **p** is independently 0 or an integer ≤ 10;

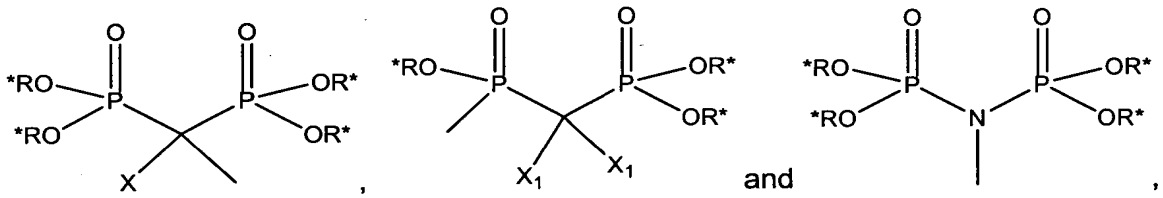
each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl;

q is 2 or 3;

X is CH_2, —CON$\mathbf{R_L}$—, —CO—O—CH_2—, or —CO—O—; and

$\mathbf{R_a}$ is C_xH_y where x is an integer of 0 to 20 and y is an integer of 1 to 2x+1.

B is a phosphonated group selected from the group consisting of:



wherein:

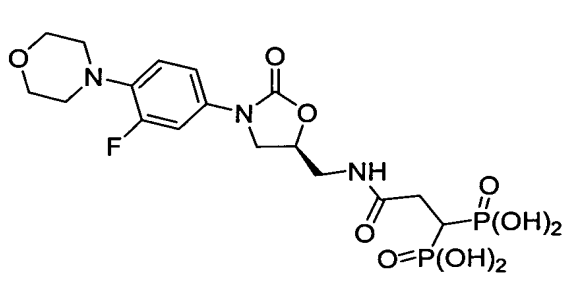
each **R*** is independently selected from the group consisting of H, lower alkyl, cycloalkyl, aryl and heteroaryl, with the proviso that at least two **R*** are H;

X is H, OH, NH_2, or a halo group;

each $\mathbf{X_1}$ is independently selected from the group consisting of H, OH, NH_2, and a halo group;

with the proviso that at least one of $\mathbf{L_1}$, $\mathbf{L_2}$, $\mathbf{L_3}$, $\mathbf{L_4}$, $\mathbf{L_5}$, $\mathbf{L_6}$, $\mathbf{L_7}$, $\mathbf{L_8}$, $\mathbf{L_9}$, $\mathbf{L_{10}}$, $\mathbf{L_{11}}$, $\mathbf{L_{12}}$, $\mathbf{L_{13}}$, $\mathbf{L_{14}}$, $\mathbf{L_{15}}$, $\mathbf{L_{16}}$, $\mathbf{L_{17}}$, $\mathbf{L_{18}}$, $\mathbf{L_{19}}$, $\mathbf{L_{20}}$, $\mathbf{L_{21}}$, $\mathbf{L_{22}}$, $\mathbf{L_{23}}$, $\mathbf{L_{24}}$ and $\mathbf{L_{25}}$ is present.

In further preferred embodiments, the compounds of the invention have a structure selected among the structures illustrated below, as well as pharmaceutically acceptable salts and prodrugs thereof:



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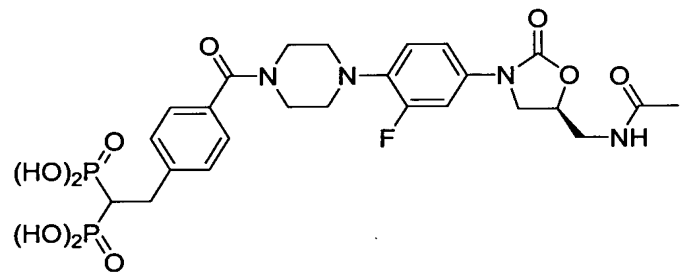

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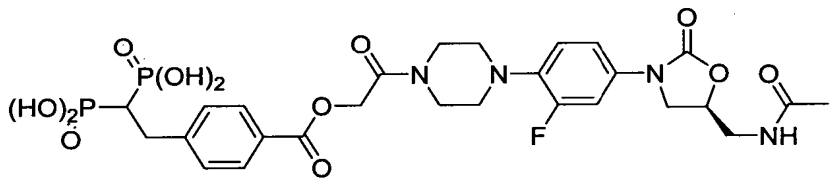

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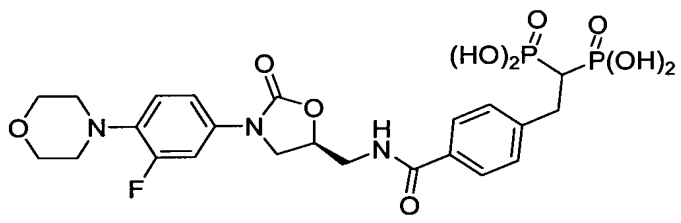

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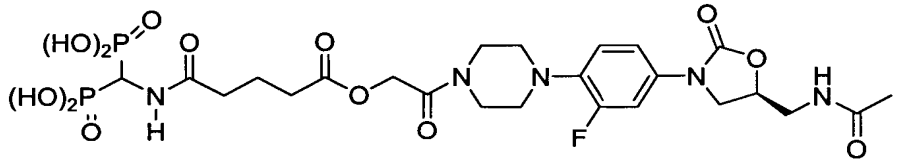

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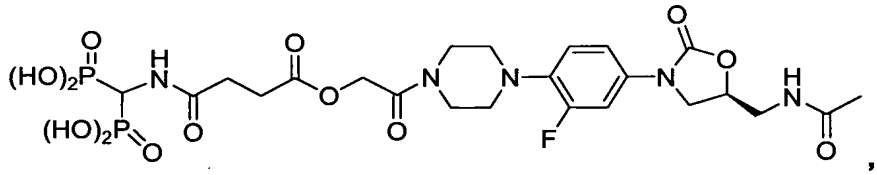

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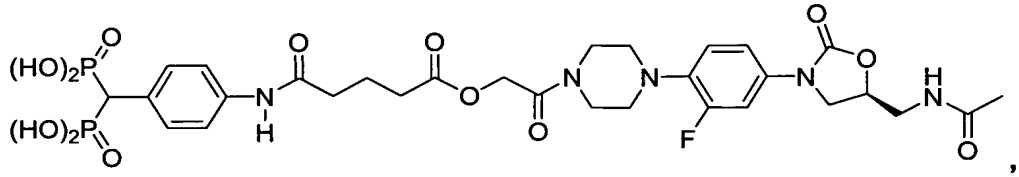

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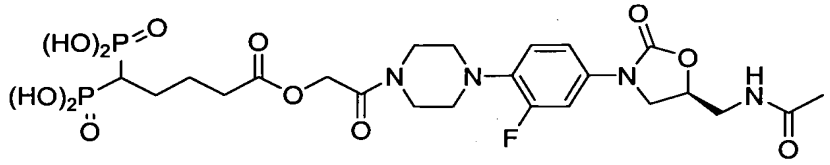

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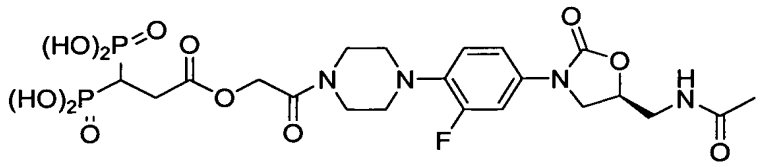

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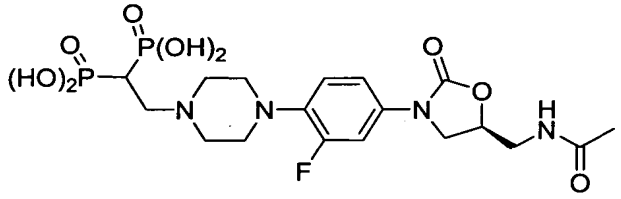

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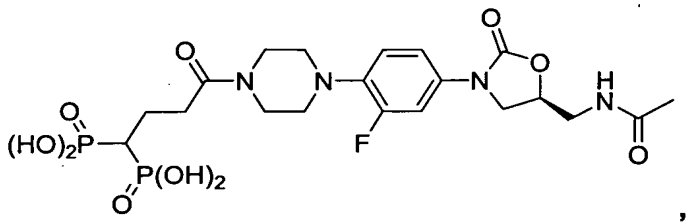

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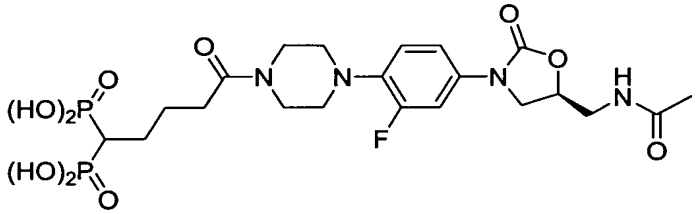

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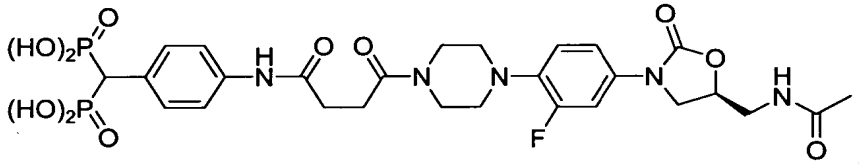

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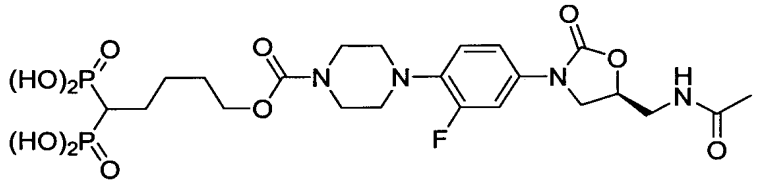

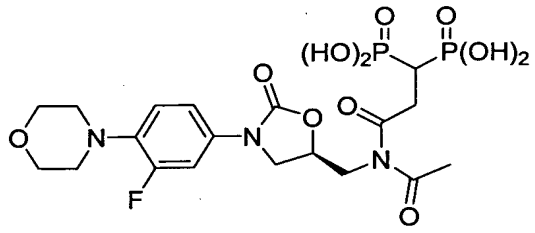

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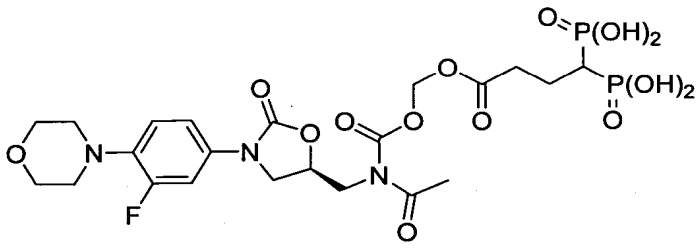


In another aspect of the present invention there are disclosed pharmaceutical compositions comprising one or more of the compounds as defined herein and a pharmaceutically acceptable carrier or excipient.

The present invention also encompasses methods for treating a bacterial infection in a subject, comprising administering to a subject having a bacterial infection or otherwise in need of such treatment a pharmaceutically effective amount of one or more of the compounds as defined herein, or a pharmaceutical composition as defined herein. The subject may be an animal, preferably a mammal, more preferably a human.

The present invention further encompasses methods for prophylaxis for a bacterial infection in a subject, comprising administering to a subject a prophylactically effective amount of one or more of the compounds as defined herein, or a pharmaceutical composition as defined herein. The prophylactically effective amount of the compounds or pharmaceutical composition may be administered to a subject prior to, during, or after an invasive medical treatment. The subject may be an animal, preferably a mammal, more preferably a human.

The present invention also encompasses methods for treating a bacterial infection in a subject, comprising administering to a subject having a bacterial infection or otherwise in need of such treatment a pharmaceutically effective amount of one or more of the compounds as defined herein, or a pharmaceutical composition as defined herein, and concurrently administering a

second therapeutic agent. Preferably the second therapeutic agent is an antibiotic. More preferably the second therapeutic agent is an antibiotic selected from the group consisting of tetracycline, a tetracycline derived antibacterial agent, glycylcycline, a glycylcycline derived antibacterial agent, minocycline, a minocycline derived antibacterial agent, an oxazolidinone antibacterial agent, an aminoglycoside antibacterial agent, a quinolone antibacterial agent, vancomycin, a vancomycin derived antibacterial agent, a teicoplanin, a teicoplanin derived antibacterial agent, eremomycin, an eremomycin derived antibacterial agent, chloroeremomycin, a chloroeremomycin derived antibacterial agent, daptomycin, a daptomycin derived antibacterial agent, Rifamycin, a Rifamycin derived antibacterial agent, Rifampin, a Rifampin derived antibacterial agent, Rifalazil, a Rifalazil derived antibacterial agent, Rifabutin, a Rifabutin derived antibacterial agent, Rifapentin, a Rifapentin derived antibacterial agent, Rifaximin and a Rifaximin derived antibacterial agent.

The invention also provides a method for accumulating oxazolidinone antimicrobial molecule in a bone of a subject, comprising administering to a subject one or more of the compounds as defined herein, or a pharmaceutical composition as defined herein. Such method for accumulating oxazolidinone antimicrobial molecules in a bone of a subject may also be used to prolong the presence of oxazolidinone antimicrobial molecule in a bone of a subject. In each instance, the subject may be an animal, preferably a mammal, more preferably a human.

In a further aspect of the present invention there are provided processes for the preparation of phosphonated oxazolidinone antimicrobial molecule , preferably oxazolidinone antimicrobial molecule of Formula (I) and/or Formula (II) as defined herein.

An advantage of the invention is that it provides antimicrobial compounds having an increased binding affinity for bone. The invention also provides methods for the unmet medical need of prevention and treatment of bone and joint infections.

Additional objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments with reference to the accompanying drawings which are exemplary and should not be interpreted as limiting the scope of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a bar graph showing increased binding affinity to ossoues materials for phosphonated derivatives **60** and **62** of oxazolidinone according to the invention.

Figure 2 is a bar graph showing readout of fluorescence (luciferase; RLU) for measuring the effect of phosphonated compounds **68**, **69**, **70**, **71**, **72**, **79** and **80** at 20 μM on *in vitro* coupled transcription-translation using *E. coli* S30 extracts with a luciferase readout.

Figure 3 is a bar graph showing amounts of selected phosphonated compounds **68**, **72**, **74** and **80** found in the femur of mice 1 h and 24 h post injection (10 mg/kg IV , 3 mice per time point).

Figure 4 is a bar graph showing the sum of drug and prodrug concentrations in plasma of rat treated with 1 mg/kg and 10mg/kg of compound **72** (IV bolus) after 1 h.

Figures 5A and **5B** are bar graphs showing combined drug and prodrug (Fig. 5A) and regenerated eperezolid (Fig. 5B) in rat tibia at 1h and 24h after an IV bolus dosage of compound **72** at 1mg/kg and 10 mg/kg

Figure 6 is a curve representing the concentration of bisphosphonated prodrug **72** and regenerated eperezolid found in rat tibia after an IV bolus dosage of compound **72** at 10 mg/kg

DETAILED DESCRIPTION OF THE INVENTION

A) General overview of the invention

The present invention discloses phosphonated derivatives of oxazolidinones of structural Formula I and Formula II as defined above. These compounds are useful antimicrobial agents effective against a number of human and veterinary pathogens.

The essence of the invention lies in the presence of a phosphonated group attached to an oxazolidinone antibiotic. Since phosphonic acid derivatives are known to have a high affinity to bone due to their ability to bind the Ca^{2+} ions found in the hydroxyapatite forming bone tissues, the present inventors have hypothesized that it would be possible to increase the binding affinity, adsorption and retention of oxazolidinone antibiotics by the bones by tethering a phosphonated group to such an antibiotic. Achieving high concentrations of oxazolidinones in vascularized bone (in comparison with the concentrations achieved by administration of a non-phosphonated antibiotic), could prove to increase the concentration of the antibiotic in contiguous devascularized bones (sequestrum) to a level sufficient to eradicate microbes present in this locus of treatment resistance.

Actually, the present inventors have synthesized such phosphonated derivatives of oxazolidinone and demonstrated that these derivatives have an increased affinity for bony materials. The present inventors have also shown that these phosphonated derivatives accumulate in bones of mammals in amounts greater than amounts of a non-phosphonated

equivalent of oxazolidinone antimicrobials and that it is possible to prolong the presence of oxazolidinone antimicrobials in the bones by administering such phosphonated derivatives. Accordingly, the compounds of the invention are particularly useful for the prevention and/or the treatment of bone-related infections and bone-related diseases such as osteomyelitis.

B) Definitions

The present invention discloses phosphonated oxazolidinone antimicrobial molecules, in particular, those phosphonated compounds defined in Formula (I) and Formula (II) as defined above and hereinafter. These compounds are useful antimicrobial agents effective against a number of human and veterinary pathogens. A phosphonated group is reversibly coupled to an oxazolidinone antimicrobial molecule via a cleavable linker.

Phosphonated oxazolidinone antimicrobial molecules have been synthesized demonstrated to have an increased affinity for osseous materials. In vivo, these phosphonated compounds accumulate in bones in amounts greater than amounts of non-phosphonated equivalents. The presence of oxazolidinone antimicrobial molecules in the bones can be prolonged by administering phosphonated derivatives of oxazolidinone antimicrobial molecules according to the invention. Accordingly, the compounds of the invention are particularly useful for the prophylaxis and/or treatment of bone and joint-related infections and bone-related diseases such as osteomyelitis.

B) Definitions

In order to provide an even clearer and more consistent understanding of the invention, including the scope given herein to particular terms, the following general definitions are provided:

The term **"alkyl"** refers to saturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms (preferably 1 to 6). Examples of alkyl groups include, but are not limited to groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, and adamantyl. Cyclic alkyl groups (e.g. cycloalkyl or heterocycloalkyl) can consist of one ring, including, but not limited to, groups such as cycloheptyl, or multiple fused rings, including, but not limited to, groups such as adamantyl or norbornyl.

The term **"alkylaryl"** refers to an alkyl group having the number of carbon atoms designated, appended to one, two, or three aryl groups.

The term "N-**alkylaminocarbonyl**" refers to the radical —C(O)NHR where R is an alkyl group.

The term "N,N-**dialkylaminocarbonyl**" refers to the radical —C(O)NR_a R_b where R_a and R_b are each independently an alkyl group.

The term "**alkylthio**" refers to the radical —SR where R is an alkyl group.

The term "**alkoxy**" as used herein refers to an alkyl, alkenyl, or alkynyl linked to an oxygen atom and having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms (preferably 1 to 6). Examples of alkoxy groups include, but are not limited to, groups such as methoxy, ethoxy, tert-butoxy, and allyloxy. The term "**alkoxycarbonyl**" refers to the radical —C(O)OR where R is an alkyl. The term "**alkylsulfonyl**" refers to the radical —SO_2 R where R is an alkyl group.

The term "**alkylene**" means a saturated divalent aliphatic group including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms (preferably 1 to 6), e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2-methyl-propylene, butylene, pentylene, cyclopentylmethylene, and the like.

The term "**substituted alkyl**" means an alkyl group as defined above that is substituted with one or more substituents, preferably one to three substituents selected from the group consisting of halogen, alkyl, aryl, alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group. The phenyl group may optionally be substituted with one to three substituents selected from the group consisting of halogen , alkyl, aryl, alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide. Examples of substituted alkyl groups include, but are not limited to —CF_3, —CF_2—CF_3, hydroxymethyl, 1- or 2-hydroxyethyl, methoxymethyl, 1- or 2-ethoxyethyl, carboxymethyl, 1- or 2-carboxyethyl, methoxycarbonylmethyl, 1- or 2-methoxycarbonyl ethyl, benzyl, pyrdinylmethyl, thiophenylmethyl, imidazolinylmethyl, dimethylaminoethyl and the like.

The term "**substituted alkylene**" means an alkylene group as defined above that is substituted with one or more substituents, preferably one to three substituents, selected from the group consisting of halogen, alkyl, aryl, alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group. The phenyl group may optionally be

substituted with one to three substituents selected from the group consisting of halogen, alkyl, aryl, alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide. Examples of substituted alkyl groups include, but are not limited to —CF_2—, —CF_2—CF_2—, hydroxymethylene, 1- or 2-hydroxyethylene, methoxymethylene, 1- or 2-ethoxyethylene, carboxymethylene, 1- or 2-carboxyethylene, and the like.

The term **"alkenyl"** refers to unsaturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms (preferably 1 to 6), which contain at least one double bond (—C=C—). Examples of alkenyl groups include, but are not limited to allyl vinyl, —CH_2—CH=CH—CH_3, —CH_2—CH_2-cyclopentenyl and —CH_2—CH_2-cyclohexenyl where the ethyl group can be attached to the cyclopentenyl, cyclohexenyl moiety at any available carbon valence.

The term **"alkenylene"** refers to unsaturated divalent aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms (preferably 1 to 6), which contain at least one double bond (—C=C—). Examples of alkenylene groups include, but are not limited to —CH=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH(cyclopentenyl)—and the like.

The term **"alkynyl"** refers to unsaturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms (preferably 1 to 6), which contain at least one triple bond (—C ≡C—). Examples of alkynyl groups include, but are not limited to acetylene, 2-butynyl, and the like.

The term **"alkynylene"** refers to unsaturated divalent aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms (preferably 1 to 6), which contain at least one triple bond (—C≡C—). Examples of alkynylene groups include, but are not limited to —C≡C—, —C≡C—CH_2—, and the like.

The term **"substituted alkenyl"** or **"substituted alkynyl"** refers to the alkenyl and alkynyl groups as defined above that are substituted with one or more substituents selected from the group consisting of halogen, alkyl, aryl, alkoxy, acyloxy, amino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the

invention, with a protecting group. Examples of substituted alkenyl and alkynyl groups include, but are not limited to —CH=CF_2, methoxyethenyl, methoxypropenyl, bromopropynyl, and the like.

The term **"substituted alkenylene"** or **"substituted alkynylene"** refers to the alkenylene and alkynylene groups as defined above that are substituted with one or more substituents selected from the group consisting of halogen, alkyl, aryl, alkoxy, acyloxy, amino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group.

The term **"aryl"** or **"Ar"** refers to an aromatic carbocyclic group of 6 to 14 carbon atoms having a single ring (including but not limited to groups such as phenyl) or multiple condensed rings (including but not limited to groups such as naphthyl or anthryl), and includes both unsubstituted and substituted aryl groups. Substituted aryl is an aryl group that is substituted with one or more substituents, preferably one to three substituents, selected from the group consisting of alkyl, aryl, alkenyl, alkynyl, halogen, alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, aryloxy, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group. Representative examples include, but are not limited to naphthyl, phenyl, chlorophenyl, iodophenyl, methoxyphenyl, carboxyphenyl, and the like. The term **"aryloxy"** refers to an aryl group linked to an oxygen atom at one of the ring carbons. Examples of alkoxy groups include, but are not limited to, groups such as phenoxy, 2-, 3-, or 4-methylphenoxy, and the like. The term **"arylthio group"** refers to the radical —SR_c where R_c is an aryl group. The term **"heteroarylthio group"** refers to the radical —SR_d where R_d is a heteroaryl.

The term **"arylene"** refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term **"amino"** refers to the group —NH_2.

The term "N-**alkylamino**" and "N,N-**dialkylamino**" means a radical —NHR and —NRR' respectively where R and R' independently represent an alkyl group as defined herein. Representative examples include, but are not limited to N,N-dimethylamino, N-ethyl-N-methylamino, N,N-di(1-methylethyl)amino, N-cyclohexyl-N-methylamino, N-cyclohexyl-N-ethylamino, N-cyclohexyl-N-propylamino, N-cyclohexylmethyl-N-methylamino, N-cyclohexylmethyl-N-ethylamino, and the like.

The term **"thioalkoxy"** means a radical —SR where R is an alkyl as defined above e.g., methylthio, ethylthio, propylthio, butylthio, and the like.

The term **"acyl group"** means a radical —C(O)R, where R is hydrogen, halogen, alkyl, aryl, heteroaryl, alkoxy, aryloxy, N-alkylamino, N,N-dialkylamino, N-arylamino, thioalkoxy, thioaryloxy or substituted alkyl wherein alkyl, aryl, heteroaryl, and substituted alkyl are as defined herein.

The term **"thioacyl group"** means a radical —C(S)R, where R is hydrogen, halogen, alkyl, aryl, heteroaryl, alkoxy, aryloxy, N-alkylamino, N,N-dialkylamino, N-arylamino, thioalkoxy, thioaryloxy or substituted alkyl wherein alkyl, aryl, heteroaryl, and substituted alkyl are as defined herein.

The term **"sulfonyl group"** means a radical —SO_2R, where R is hydrogen, halogen, alkyl, aryl, heteroaryl, alkoxy, aryloxy, N-alkylamino, N,N-dialkylamino, N-arylamino, thioalkoxy, thioaryloxy or substituted alkyl wherein alkyl, aryl, heteroaryl, and substituted alkyl are as defined herein.

The term **"acyloxy"** means a radical —OC(=O)R, where R is hydrogen, alkyl, aryl, heteroaryl or substituted alkyl wherein alkyl, aryl, heteroaryl, and substituted alkyl are as defined herein. Representative examples include, but are not limited to formyloxy, acetyloxy, cylcohexylcarbonyloxy, cyclohexylmethylcarbonyloxy, benzoyloxy, benzylcarbonyloxy, and the like.

The term **"heteroalkyl," "heteroalkenyl,"** and **"heteroalkynyl"** refers to alkyl, alkenyl, and alkynyl groups respectively as defined above, that contain the number of carbon atoms specified (or if no number is specified, having 1 to 12 carbon atoms, preferably 1 to 6) which contain one or more heteroatoms, preferably one to three heteroatoms, as part of the main, branched, or cyclic chains in the group. Heteroatoms are independently selected from the group consisting of —NR—, —NRR, —S—, —S(O) —, —$S(O)_2$—, —O—, —SR, —S(O)R, —$S(O)_2R$, —OR —PR—, —PRR, —P(O)R— and —P(O)RR; (where each R is hydrogen, alkyl or aryl) preferably —NR where R is hydrogen or alkyl and/or O. Heteroalkyl, heteroalkenyl, and heteroalkynyl groups may be attached to the remainder of the molecule either at a heteroatom (if a valence is available) or at a carbon atom. Examples of heteroalkyl groups include, but are not limited to, groups such as —O—CH_3, —CH_2—O—CH_3, —CH_2—CH_2—O—CH_3, —S—CH_2—CH_2—CH_3, —CH_2—$CH(CH_3)$—S—CH_3, —CH_2—CH_2—NH—CH_2—CH_3, 1-ethyl-6-propylpiperidino, 2-ethylthiophenyl, piperazino, pyrrolidino, piperidino, morpholino, and the like. Examples of heteroalkenyl groups include, but are not limited to groups such as —CH=CH-CH_2—$N(CH_3)_2$, and the like.

The term **"heteroaryl"** or **"HetAr"** refers to an aromatic monovalent monocyclic, bicyclic, or tricyclic radical containing 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 -member ring atoms, including 1, 2, 3, 4, or 5 heteroatoms, preferably one to three heteroatoms including, but

not limited to heteroatoms such as N, O, P, or S, within the ring. Representative examples include, but are not limited to single ring such as imidazolyl, pyrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, pyridyl, thiophene, and the like, or multiple condensed rings such as indolyl, quinoline, quinazoline, benzimidazolyl, indolizinyl, benzothienyl, and the like.

The heteroalkyl, heteroalkenyl, heteroalkynyl and heteroaryl groups can be unsubstituted or substituted with one or more substituents, preferably one to three substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, benzyl, halogen, alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, aryloxy, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group. Examples of such substituted heteroalkyl groups include, but are not limited to, piperazine, pyrrolidine, morpholine, or piperidine, substituted at a nitrogen or carbon by a phenyl or benzyl group, and attached to the remainder of the molecule by any available valence on a carbon or nitrogen, —NH—$S(=O)_2$—phenyl, —NH—(C=O)O-alkyl, —NH—C(=O)O-alkyl-aryl, and the like. The heteroatom(s) as well as the carbon atoms of the group can be substituted. The heteroatom(s) can also be in oxidized form.

The term **"heteroarylene"** refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridinylene, 2,4-pyridinylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridinylene, 2,5-indolenylene, and the like.

The term **"heteroalkylene"**, **"heteroalkenylene"**, and **"heteroalkynylene"** refers to the diradical group derived from heteroalkyl, heteroalkenyl, and heteroalkynyl (including substituted heteroalkyl, heteroalkenyl, and heteroalkynyl) as defined above.

The term **"carboxaldehyde"** means —CHO.

The term **"carboalkoxy"** means —C(=O)OR where R is alkyl as defined above and include groups such as methoxycarbonyl, ethoxycarbonyl, and the like.

The term **"carboxamide"** means —C(=O)NHR or —C(=O)NRR' where R and R' are independently hydrogen, aryl or alkyl as defined above. Representative examples include groups such as aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, and the like.

The term **"carboxy"** refers to the radical —C(O)OH.

The term **"carbamoyl"** refers to the radical —$C(O)NH_2$.

The term **"halogen"** or **"halo"** as used herein refer to Cl, Br, F or I substituents, preferably fluoro or chloro.

The term **"hydroxy"** refers to a —OH radical.

"**Isomers**": Compounds that have the same molecular formula (or elemental composition) but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers in which the connectivity between atoms is the same but which differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example which is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn, Ingold and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either an individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers. Such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. For example, each of compounds **6** and **17** as described in the Exemplification section possesses a carbon (carbon 5 of the oxazolidinone ring) linked to a hydrogen atom, an oxygen atom, and two different methylene groups, and therefore these carbons are asymmetric centers. The compounds **6** and **17** can exist as stereoisomers. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The description is also intended to include all possible diastereomers and mixtures thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

"**Optically pure**": As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term "optically pure" is intended to mean a compound which comprises at least a sufficient amount of a single enantiomer to yield a compound having the desired pharmacological activity. Preferably, "optically pure" is intended to mean a compound that comprises at least 90% of a single isomer (80% enantiomeric excess), preferably at least 95% (90% e.e.), more preferably at least 97.5% (95% e.e.), and most preferably at least 99% (98% e.e.). Preferably, the compounds of the invention are optically pure.

"**Protecting group**" refers to a chemical group that exhibits the following characteristics: 1) reacts selectively with the desired functionality in good yield to give a protected substrate that

is stable to the projected reactions for which protection is desired; 2) is selectively removable from the protected substrate to yield the desired functionality; and 3) is removable in good yield by reagents compatible with the other functional group(s) present or generated in such projected reactions. Examples of suitable protecting groups can be found in Greene et al. (1991) Protective Groups in Organic Synthesis, 2nd Ed. (John Wiley & Sons, Inc., New York). Preferred amino protecting groups include, but are not limited to, benzyloxycarbonyl (CBz), t-butyloxycarbonyl (Boc), t-butyldimethylsilyl (TBDMS), 9-fluorenylmethyl-oxycarbonyl (Fmoc), or suitable photolabile protecting groups such as 6-nitroveratryloxy carbonyl (Nvoc), nitropiperonyl, pyrenylmethoxycarbonyl, nitrobenzyl, dimethyl dimethoxybenzil, 5-bromo-7-nitroindolinyl, and the like. Preferred hydroxyl protecting groups include acetyl (Ac), benzoyl (Bz), benzyl (Bn), Tetrahydropyranyl (THP), TBDMS, photolabile protecting groups (such as nitroveratryl oxymethyl ether (Nvom)), Mom (methoxy methyl ether), and Mem (methoxy ethoxy methyl ether). Particularly preferred protecting groups include NPEOC (4-nitrophenethyloxycarbonyl) and NPEOM (4-nitrophenethyloxy-methyloxycarbonyl).

"Prodrug": Phosphonated oxazolidinone antimicrobial molecules of the present invention may be formulated as prodrugs. According to the present invention, a prodrug is an inactive (or significantly less active) form of any of the phosphonated oxazolidinone antimicrobial molecule compounds of the present invention. Upon *in vivo* processing, prodrugs of the present invention release an active phosphonated oxazolidinone antimicrobial molecule. Prodrugs of phosphonated oxazolidinone antimicrobial molecules of the present invention may be prepared by modifying functional groups present on the phosphonated oxazolidinone antimicrobial molecules in such a way that the modifications may be cleaved *in vivo* to release the oxazolidinone antimicrobial molecules.

Prodrugs include compounds of Formula (I) and/or Formula (II) wherein a hydroxy or amino group in the oxazolidinone antimicrobial molecule portion of the compound is bonded to any group that may be cleaved *in vivo* to regenerate the free carboxyl or amino group, respectively. Such prodrug groups are in addition to the phosphonated linker that may be coupled to a hydroxy and/or amino group of an oxazolidinone antimicrobial molecule. Examples of prodrug groups include, but are not limited to, esters (e.g., acetate, formate, and benzoate derivatives) and carbamates (e.g., N,N-dimethylaminocarbonyl) on hydroxy functional groups of the oxazolidinone antimicrobial molecule portion of the phosphonated compounds of the present invention. The present invention also includes those prodrugs requiring two or more events in prodrug cleavage. According to that embodiment, more complex compounds would release, upon cleavage, a prodrug of phosphonated oxazolidinone antimicrobial molecule, the latter prodrug being activatable to release a desired phosphonated oxazolidinone antimicrobial

molecule. The skilled artisan will understand that prodrugs of phosphonated oxazolidinone antimicrobial molecules of the present invention may undergo two cleavage events, one of which cleaves the cleavable linker and thus releases the phosphonate group, the other of which results in the release of the prodrug group.

A **"pharmaceutically acceptable prodrug"** is intended to mean prodrug of phosphonated oxazolidinone antimicrobial molecule, such as a prodrug of a compound of Formula (I) and/or Formula (II), in a formulation that may be administered to a subject, such as a mammal, preferably a human. For example, the prodrug may be in a formulation comprising a pharmaceutically acceptable carrier or excipient.

A **"pharmaceutically acceptable active metabolite"** is intended to mean a pharmacologically active product produced through metabolism in the body of a compound of Formula (I) or Formulae (II) as defined herein.

A **"pharmaceutically acceptable solvate"** is intended to mean a solvate that retains the biological effectiveness and properties of the biologically active components of compounds of Formula I and/or Formula II. Examples of pharmaceutically acceptable solvates include, but are not limited to water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine.

A **"pharmaceutically acceptable carrier or excipient"** means any compound, solution, substance or material that can be used in a formulation of the compounds of the present invention that may be administered to a subject. In particular, carriers and excipients of the present invention are those useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and that may present pharmacologically favorable profiles and that includes carriers and excipient that are acceptable for veterinary use as well as human pharmaceutical use. Suitable pharmaceutically acceptable carriers and excipients are well known in art and can be determined by those of skill in the art as the clinical situation warrants. The skilled artisan will understand that diluents are includes within the scope of the terms carriers and excipients. Examples of suitable carriers and excipients include saline, buffered saline, dextrose, water, glycerol, ethanol, more particularly: (1) Dulbecco's phosphate buffered saline, pH about 7.4, containing about 1 mg/ml to 25 mg/ml human serum albumin, (2) 0.9% saline (0.9% w/v NaCl), (3) 5% (w/v) dextrose, and (4) water.

A **"pharmaceutically acceptable salt"** is intended to mean a salt of phosphonated oxazolidinone antimicrobial molecule, such as a salt of a compound of Formula (I) and/or Formula (II), in a formulation that may be administered to a subject, such as a mammal, preferably a human. For example, the salt may be in a formulation comprising a pharmaceutically acceptable carrier or excipient.

"**Salt**": Phosphonated oxazolidinone derived antimicrobial molecules of the present invention may be in the form of a salt. Salts of phosphonated oxazolidinone antimicrobial molecules of the present invention means a salt that retains or improves the biological effectiveness and properties of the free acids and bases of the parent compound as defined herein or that takes advantage of an intrinsically charged functionality on the molecule and that is not biologically or otherwise undesirable. Such salts include the following:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-napthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 3-phenyl propionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynapthoic acid, salicylic acid, stearic acid, muconic acid, and the like;

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like; or

(3) salts formed when a charged functionality is present on the molecule and a suitable counterion is present, such as a tetraalkyl(aryl)ammonium functionality and an alkali metal ion, a tetraalkyl(aryl)phosphonium functionality and an alkali metal ion, an imidazolium functionality and an alkali metal ion, and the like.

As used herein, the terms "**bone**", "**bone tissues**" or "**osseous tissues**" refer to the dense, semi rigid, porous, calcified connective tissue forming the major portion of the skeleton of most vertebrates. It also encompasses teeth, osteo-articular tissues and calcifications that are frequently seen in the walls of atherosclerotic vessels.

As used herein, the terms "**bone**", "**bone tissues**" or "**osseous tissues**" refer to the dense, semi rigid, porous, calcified connective tissue forming the major portion of the skeleton of most vertebrates. It also encompasses teeth, osteo-articular tissues and calcifications that are frequently seen in the walls of atherosclerotic vessels.

The term "**oxazolidinone antimicrobial molecule**" and related terms have the same meaning and refer to antimicrobial agents which are part of the well known class of "**oxazolidinones**" as described in more detail herein.

The term **"phosphonated group"** is intended to mean any compound non-toxic to humans having at least one phosphorus atom bonded to at least three oxygen atoms and having a measurable affinity to osseous tissues as described hereinafter.

The term **"antibacterial"** includes those compounds that inhibit, halt or reverse growth of bacteria, those compounds that inhibit, halt, or reverse the activity of bacterial enzymes or biochemical pathways, those compounds that kill or injure bacteria, and those compounds that block or slow the development of a bacterial infection.

The terms **"treating"** and **"treatment"** are intended to mean at least the mitigation of a disease condition associated with a bacterial infection in a subject, including mammals such as a human, that is alleviated by a reduction of growth, replication, and/or propagation of any bacterium such as Gram-positive organisms, and includes curing, healing, inhibiting, relieving from, improving and/or alleviating, in whole or in part, the disease condition.

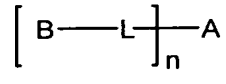
The term **"prophylaxis"** is intended to mean at least a reduction in the likelihood that a disease condition associated with a bacterial infection will develop in a mammal, preferably a human. The terms **"prevent"** and **"prevention"** are intended to mean blocking or stopping a disease condition associated with a bacterial infection from developing in a mammal, preferably a human. In particular, the terms are related to the treatment of a mammal to reduce the likelihood (**"prophylaxis"**) or prevent the occurrence of a bacterial infection, such as bacterial infection that may occur during or following a surgery involving bone reparation or replacement. The terms also include reducing the likelihood (**"prophylaxis"**) of or preventing a bacterial infection when the mammal is found to be predisposed to having a disease condition but not yet diagnosed as having it. For example, one can reduce the likelihood or prevent a bacterial infection in a mammal by administering a compound of Formula (I) and/or Formula (II), or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof, before occurrence of such infection.

The term **"subject"** is intended to mean an animal, such as a mammal, including humans and animals of veterinary importance, such as dogs, cats, horses, sheep, goats, and cattle.

B) Compounds of the invention

As will be described hereinafter in the Exemplification section, the inventors have prepared phosphonated derivatives of oxazolidinones having a high binding affinity to osseous tissues.

In one embodiment, the compounds of the invention are represented by the general Formula (I):



(I)

as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

A is an oxazolidinone antimicrobial molecule;

B is a phosphonated group having a high affinity to osseous tissues;

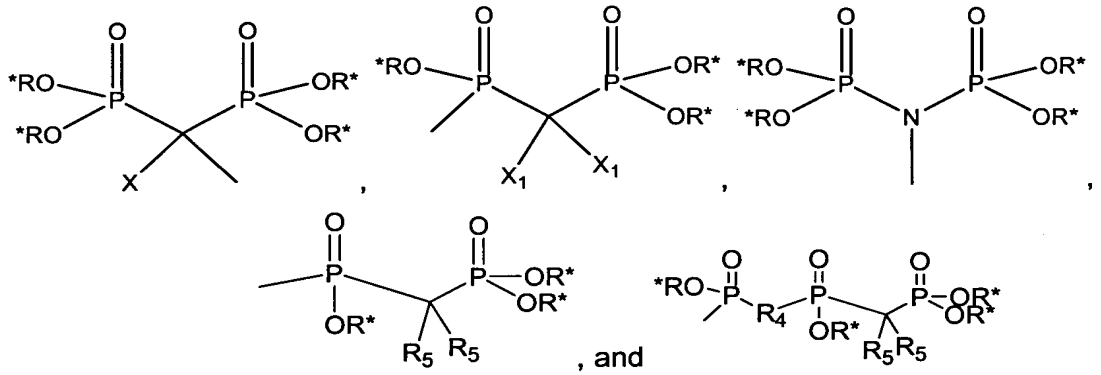
L is a bond or a linker for covalently coupling B to A; and

n is an 1,2 or 3.

As mentioned previously, the essence of the invention lies in the presence of a phosphonated group attached to an oxazolidinone antibiotic for increasing the affinity, binding, accumulation and/or retention time of the oxazolidinone antibiotic to or within the bones.

Phosphonates

All non-toxic phosphonated groups having a high affinity to the bones due to their ability to bind the Ca^{2+} ions found in the hydroxyapatite forming the bone tissues are suitable according to the present invention. Suitable examples of phosphonated groups can be found in WO 04/026315 (Ilex Oncology Research), US 6,214,812 (MBC research), US 5,359,060 (Pfizer), US 5,854,227 and US 6,333,424 (Elizanor), US 6,548,042 (Arstad and Skattelbol) and WO 2004/089925 (Semaphore Pharmaceuticals). Examples of bisphosphonate and trisphosphonate groups suitable for the present invention include but are not limited to those having the formula:



, and

wherein:

each **R*** is independently selected from the group consisting of H, lower alkyl, cycloalkyl, aryl and heteroaryl, with the proviso that at least two, preferably three, **R*** are H;

$\mathbf{R_4}$ is CH_2, O, S, or NH;

each $\mathbf{R_5}$ is independently selected from the group consisting of H, $\mathbf{R_6}$, $\mathbf{OR_6}$, $\mathbf{NR_6}$, and $\mathbf{SR_6}$, wherein $\mathbf{R_6}$ is H, lower alkyl, cycloalkyl, aryl, heteroaryl or NH_2;

X is H, OH, NH_2, or a halo group; and

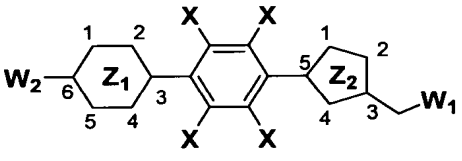
$\mathbf{X_1}$ are both H, or each is independently selected from the group consisting of H, OH, NH_2, and a halo group.

Although monophosphonates, bisphosphonates, and tris- or tetraphosphonates could potentially be used, bisphosphonates are preferred. More preferably, the bisphosphonate group is the bisphosphonate $-CH(P(O)(OH)_2)_2$. As shown in Example 2 hereinafter, oxazolidinone derivatives possessing such a bisphosphonate group have a strong binding affinity for hydroxyapatite powder. Of course, other types of phosphonated group could be selected and synthesized by those skilled in the art. For instance the phosphonated group may be an esterase-activated bisphosphonate radical (Vepsäläinen J., Current Medicinal Chemistry, 9, 1201-1208, 2002) or be any other suitable prodrug thereof. These and other suitable phosphonated groups are encompassed by the present invention.

Oxazolidinones

Oxazolidinones are a well known class of synthetic Gram-positive antimicrobial agents (see for example U.S. Pat. Nos. 5,652,238; 5,688,792; 5,529,998; 5,547,950; 5,627,181; 5,700,799; 5,843,967; 5,792,765; 5,684,023; 5,861,413; 5,827,857; 5,869,659; 5,698,574; 5,968,962; 5,981,528; US 6,638,955; US 6,365,751; US 6,271,383; US 5,981,528; and PCT patent applications WO 95/0727, WO 95/14684, WO 99/24393, WO 03/072575, and WO 03/072576). Linezolid [(*S*)-*N*-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide] and eperezolid [(*S*)-*N*-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide] are certainly the best known compounds in this class. Both drugs were proven clinically and microbiologically to have potent activity against Gram-positive organisms. The present invention is not restricted to a specific oxazolidinone, but encompasses all kinds of oxazolidinone molecules having a suitable antimicrobial activity including, but not limited to, those disclosed in the above-listed US patents and PCT patent applications (incorporated herein by reference) and other oxazolidinone derivatives and hybrids such as the oxazolidinone-quinolone hybrids disclosed by Morphochem Inc. (Gordeev *et al.*, Bioorg.Med.Chem.Lett. (2003),13:4213-16) or by Vicuron Pharmaceuticals (Hubschewerlen *et al.*, Bioorg.Med.Chem.Lett. (2003) 13 :4229-33).

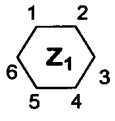
According to a preferred embodiment, the term **"oxazolidinone antimicrobial molecule"** includes all compounds having the Formula A_1 illustrated below:



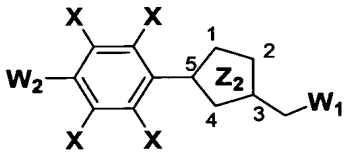
(A1)

as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

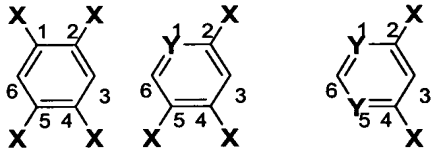
Each of **X** is independently hydrogen or a halogen, preferably a hydrogen or fluorine;



is either absent, in which case A_1 becomes



or is selected from the group consisting of formulae **M1-M3**

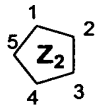


M1 , **M2** and **M3**

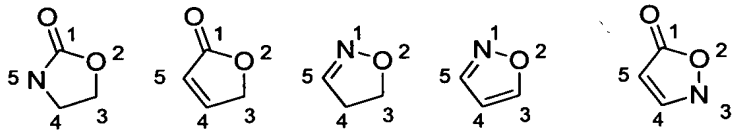
Wherein:

each **X** is defined as above;

each **Y** is independently N or CH



is selected from the group consisting of formulae **M4-M8**



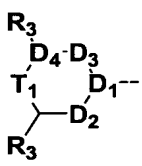
M4 , **M5** , **M6** , **M7** and **M8**

W_1 is hydroxy, halo, amino, azido, (1-4C)alkanesulfonyloxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, $NHS(O)_m$(1-4C)alkyl, $NHCOR_c$, $NHCSR_c$; isoxazol-3-oxy, isothiazol-3-oxy, (1,2,5-thiadiazol)-3-oxy, (1,2,5-oxadiazol)-3-oxy, isoxazol-3-amino,

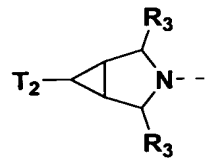
isothiazol-3- amino, (1,2,5-thiadiazol)-3- amino, (1,2,5-oxadiazol)-3-amino, tetrazol-2-yl, tetrazol-1-yl, (1,2,3-triazol)-1-yl, or (4-ethynyl-1,2,3-triazol)-1-yl

wherein: **m** is 0, 1, or 2 and $\mathbf{R_c}$ is H, (1-4C)alkyl, (1-4C)dihaloalkyl, (1-4C)alkoxy, methoxymethyl, acetylmethyl, methylamino or dimethylamino;

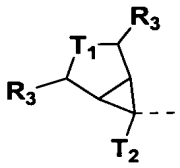
$\mathbf{W_2}$ is selected from the group consisting of formulae **M9-M16**



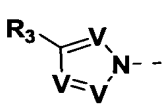
M9



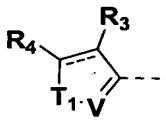
M10



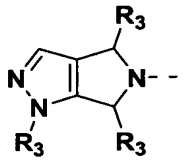
M11



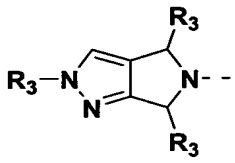
M12



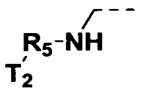
M13



M14



M15 and



M16

$\mathbf{D_1}$, is independently CH or N and $\mathbf{D_2}$, $\mathbf{D_3}$ and $\mathbf{D_4}$, are each independently CH, CH_2, N, S or O and each ⎓ represents either a single bond or a double bond;

$\mathbf{R_3}$ are each independently H, CH_3, CN, hydroxyl, bromo, oxo (=O), (1-4C)alkyl, (1-4C)alkylamino, (1-4C)alkoxycarbonyl or CO_2R_d, wherein $\mathbf{R_d}$ is H, (1-5C)alkyl, phenyl, or heteroaryl;

$\mathbf{T_1}$ is O, S, SO, SO_2, NH, NR_a, $NCOCH_2OH$, or $NCOR_a$, $C(OH)CH_2N(R_a)_2$, $C(OH)CH_2OR_a$, CH-(tetrazol-2-yl), or CH(tetrazol-1-yl)

wherein each $\mathbf{R_a}$ is independently H, aryl, (1-4C)alkyl, cycloalkyl, heteroaryl, amino, (1-4C)alkylamino, or OR_b, wherein $\mathbf{R_b}$ is (1-6C)alkyl

$\mathbf{T_2}$ is hydroxyl, amino, chloro, fluoro, bromo, $-CO_2H$, cyano, or $-C(O)N(R_d)_2$, wherein each R_d is defined as above.

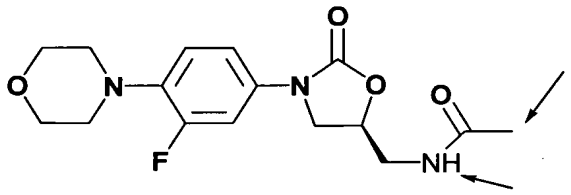
V is N or CH

$\mathbf{R_4}$ is H or (1-4C) alkyl, $-(CH_2)_x-(CH(OH))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NH_2))-(CH_2)_y-Q$ or $-(CH_2)_x-C(O)-(CH_2)_y-Q$, wherein x and y are independently 0,1 or 2 and Q is $N(R_d)_2$, imidazol-1-yl, 2-methyl-imidazol-1-yl, tetrazol-2-yl, or (1,2,3-triazol)-1-yl, with R_d defined as above.

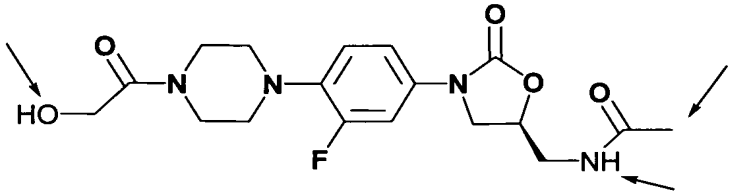
R_5 is one of either $-C_aH_b$, $-(CH_2)_a-(CH(OH))-(CH_2)_c-$, $-(CH_2)_a-(CH(NH_2))-(CH_2)_c-$, $-(CH_2)_a-(CH(OH))-(CH_2)_c-C(O)-$, or $-(CH_2)_a-(CH(NH_2))-(CH_2)_c-C(O)-$, wherein a is an integer ≥ 0 and ≤ 10, b is an integer and ≥ 0 and $\leq 2a$ and c is 0,1 or 2.

Those skilled in the art will readily identify and prepare the suitable oxazolidinone antimicrobial molecules according to the invention. If necessary they could refer to the numerous literature found in the art, including the US patents and PCT patent applications listed hereinbefore, and more particularly to International PCT patent applications WO 95/07271 and WO 95/14684, and US patent No. 5,837,870.

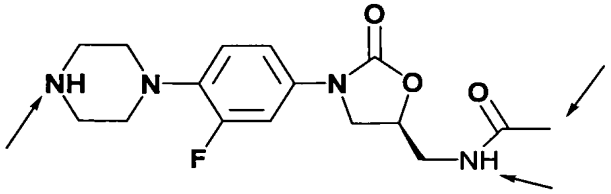
According to one embodiment, the oxazolidinone antimicrobial molecule is a derivative of linezolid. According to another embodiment, the oxazolidinone antimicrobial molecule is a derivative of eperezolid. According to a third embodiment, the oxazolidinone antimicrobial molecule is a derivative of N-((3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (eperezolid amine), as defined below. The chemical structures of these three molecules are illustrated hereinafter. Arrows indicate preferred sites for attachment of the phosphonated group (direct attachment or via an optional linker):



Linezolid



Eperezolid



Eperezolid amine

Specific examples of linezolid, eperezolid and eperezolid amine derivatives according to the invention are shown in the Exemplification section. Even though in the examples phosphonated groups have not been attached to all the preferred attachment sites shown by the arrows, the results presented in the Exemplification section confirm that it is possible to synthesize phosphonated biologically active linezolid and eperezolid derivatives having a highly increased affinity for bony materials. Similarly, although not tested, the invention encompasses phosphonated oxazolidinone derivatives having more than just one phosphonated group (one at each end of the eperezolid molecule for instance). As mentioned previously, the above identified sites of attachment are only preferred sites for tethering a phosphonated group and all other potential sites (on the aryl ring for instance) are covered by the present invention.

Linkers

A cleavable linker **L** covalently and reversibly couples the phosphonated group **B** to oxazolidinone antimicrobial molecules **A**. As used herein, the term "cleavable" refers to a group that is chemically or biochemically unstable under physiological conditions. The chemical instability preferably results from spontaneous decomposition due to a reversible chemical process, an intramolecular chemical reaction or hydrolysis (i.e. splitting of the molecule or group into two or more new molecules or groups due to the net insertion of one or more water molecules) when it depends on an intermolecular chemical reaction.

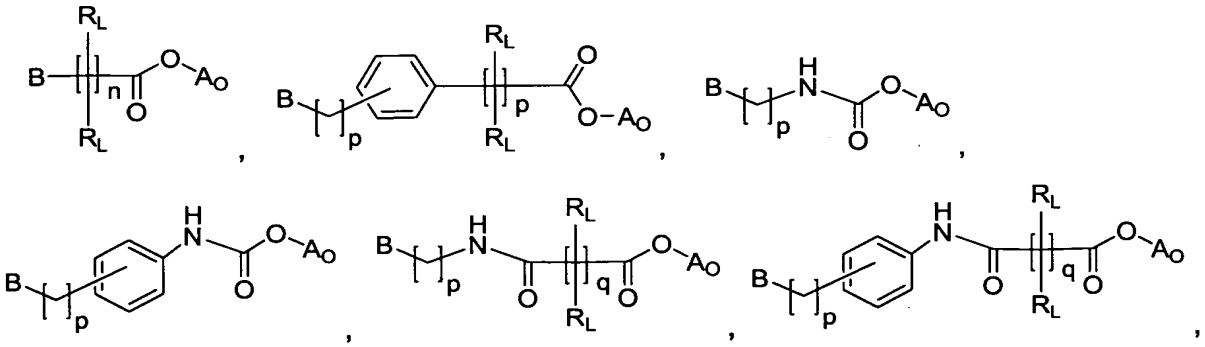
Cleavage of the linker may be very rapid or very slow. For instance, the half-life of the cleavable liker may be of about 1 minute, about 15 minutes, about 30 minutes, about 1 hour, about 5 hours, about 10 hours, about 15 hours, about 1 day or about 48 hours. The cleavable linker may be an enzyme-sensitive linker that is cleavable only by selected specific enzymes (e.g. amidase, esterase, metalloproteinase, etc) or may be susceptible to cleavage by other chemical means, such as but not limited to acid/base catalysis or self-cleavage. For instance, it is conceivable according to the invention to have an esterase-sensitive linker that is cleavable only by bone-specific esterases (Goding *et al.* Biochim Biophys Acta (2003), 1638(1):1-19) or bone-specific metalloproteinase (MMP) (Kawabe *et al.*, Clin Orthop. (1986) 211:244-51; Tuckermann *et al.*, Differentiation (2001), 69(1):49-57; Sellers *et al.*, Biochem J. (1978) 171(2):493-6) or by the action of alkaline phosphatases thereby releasing the oxazolidinone antibiotic at its desired site of action. Similarly, it is conceivable to use a cleavable linker which is not too easily cleavable in the plasma, thereby permitting a sufficient amount of the phosphonated oxazolidinone antimicrobial molecules to reach and accumulate within the osseous tissues before being cleaved to release the oxazolidinone antimicrobial molecules. For instance, the linker may be selected such that only 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%,

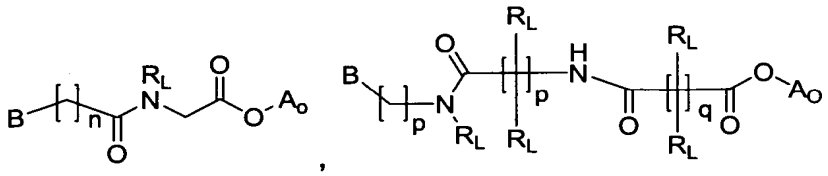
40%, 50%, 60%, or 70% of the bone-bonded antibiotic is released through a time period extending to 1 minute, 15 minutes, 30 minutes, 1 hour, 5 hours, 10 hours, 15 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days 7 days, one week, two weeks, three weeks or more following administration of the compound of the invention. Preferably, the linker is selected such that only about 1% to about 25% of the bone-bonded oxazolidinone antimicrobial molecule is released per day. The choice of the linker may vary according to factors such as (i) the site of attachment of the phosphonated group to the oxazolidinone antimicrobial molecule, (ii) the type of phosphonated group used; (iii) the type of oxazolidinone antimicrobial molecule used, and (iv) the desired ease of cleavage of the linker and associated release of the oxazolidinone antimicrobial molecule.

Preferably, the linker **L** couples the phosphonated group **B** to an oxazolidinone antimicrobial molecule **A** through one or more hydroxyl groups on **A**, through one or more nitrogen atoms on **A**, through one or more sulhydryl groups on **A**, or a combination of one or more hydroxyl groups, one or more nitrogen atoms, and/or one or more sulhydryl groups, on **A**. Between 1 and 3 phosphonated groups may be coupled to **A** through any combination of linkers **L**.

The linker is facultative because its presence is dependent upon (i) the site of attachment of the phosphonated group to the oxazolidinone molecule, (ii) the type of phosphonated group used; (iii) the type of oxazolidinone used, and (iv) the desired ease of cleavage of the linker and associated release of the oxazolidinone antibiotic. For instance, as is shown in the Exemplification section, it is possible to avoid the linker and tether a phosphonated group directly to the acetamide group of linezolid (compounds **54** and **56**).

When **L** couples **B** to **A** through a hydroxyl group on **A**, preferably **L** is one of the following linkers:

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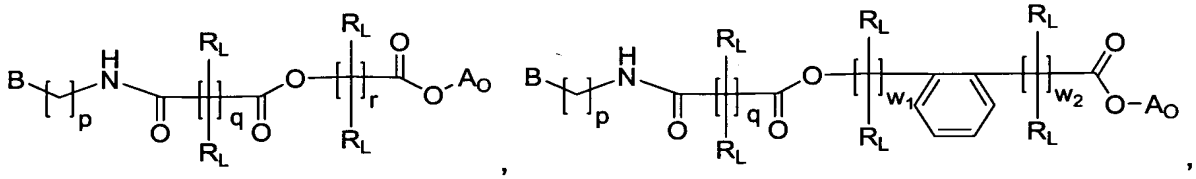
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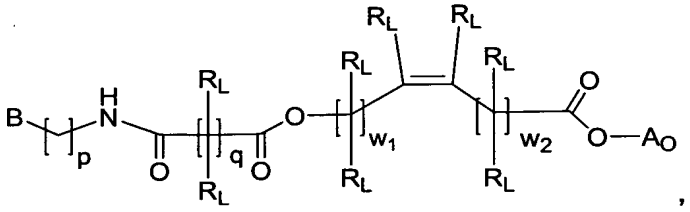
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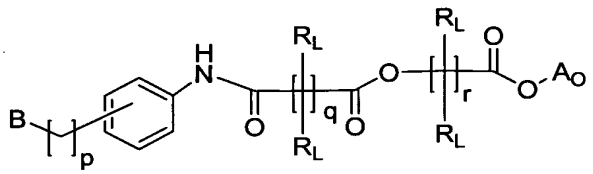
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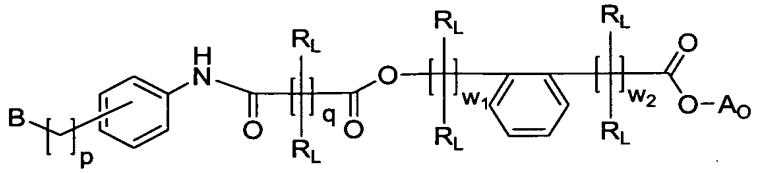
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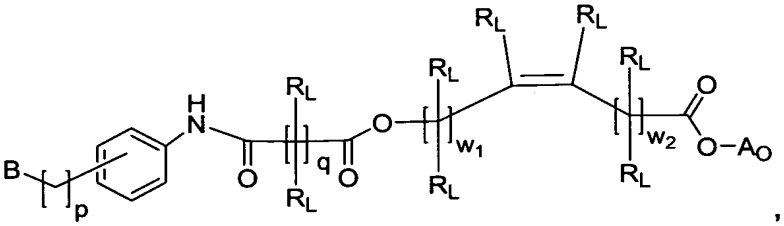
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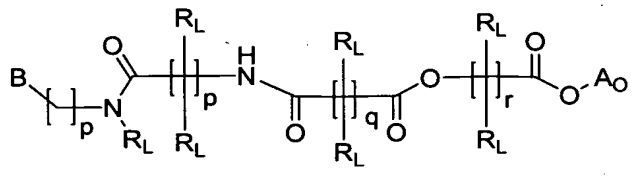
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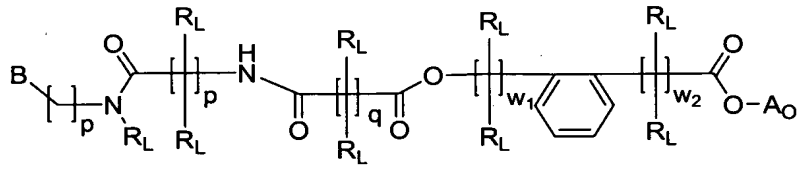
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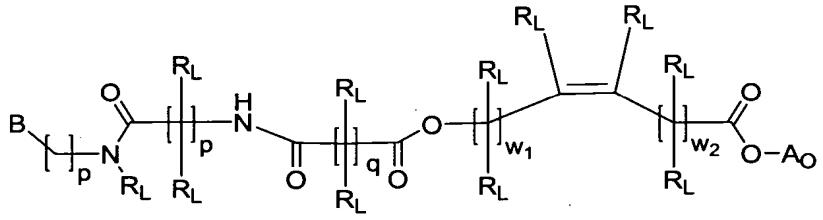


wherein:

n is an integer ≤ 10, preferably 1, 2, 3 or 4, more preferably 1 or 2;

each **p** is independently 0 or an integer ≤ 10, preferably 0, 1, 2, 3 or 4, more preferably 0 or 1;

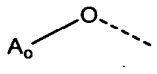
q is 2 or 3

r is 1, 2, 3, 4 or 5

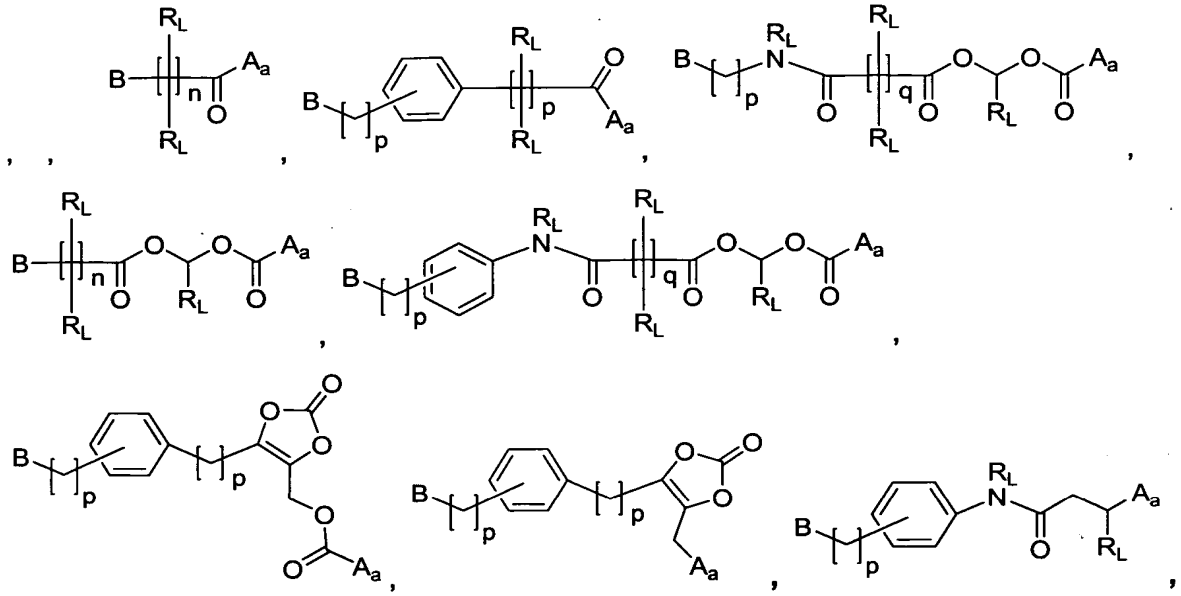
$\mathbf{w_1}$ and $\mathbf{w_2}$ are integers ≥ 0 such that their sum ($\mathbf{w_1} + \mathbf{w_2}$) is 1,2 or 3

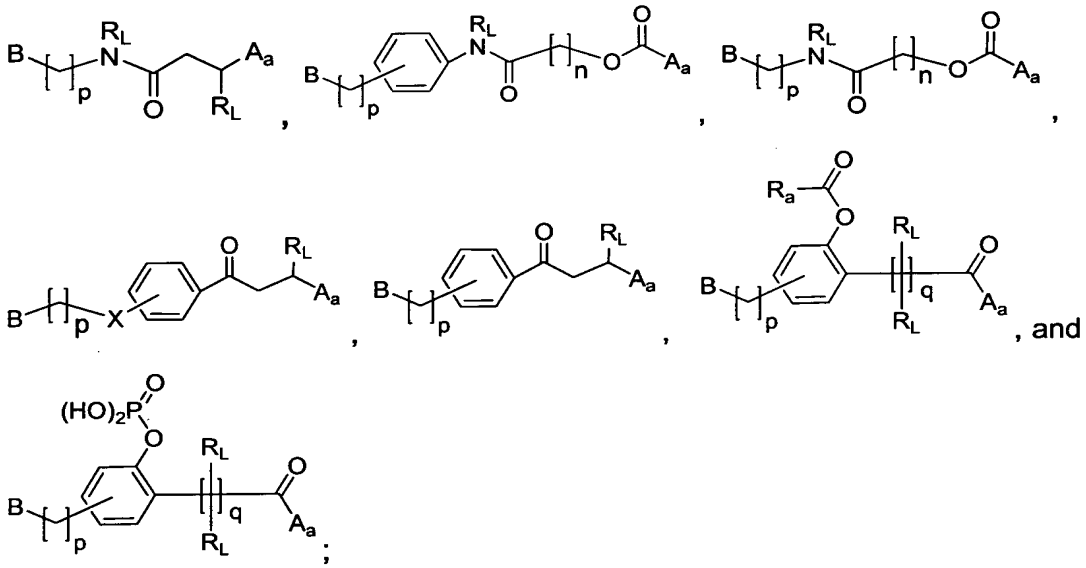
each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl, preferably H;

B represents the phosphonated group;

and the substructure  of the linker represents the hydroxyl moiety of **A**

When **L** couples **B** to **A** through a nitrogen atom on **A**, preferably **L** is one of the following linkers:





wherein:

n is an integer ≤ 10, preferably 1, 2, 3 or 4, more preferably 1 or 2;

each **p** is independently 0 or an integer ≤ 10, preferably 0, 1, 2, 3 or 4, more preferably 0 or 1;

q is 2 or 3;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl, preferably H;

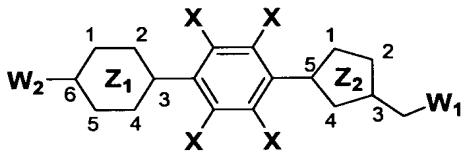
$\mathbf{R_a}$ is C_xH_y where x is an integer of 0 to 20 and y is an integer of 1 to 2x+1;

X is CH_2, —CONR$_L$—, —CO—O—CH_2—, or —CO—O—;

B represents the phosphonated group; and

$\mathbf{A_a}$ represents the nitrogen atom on **A**.

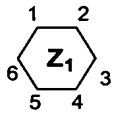
According to another particular embodiment, the compounds of the invention are represented by Formula (II) or a pharmaceutically acceptable salt or prodrug thereof:



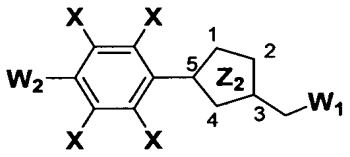
(II)

as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

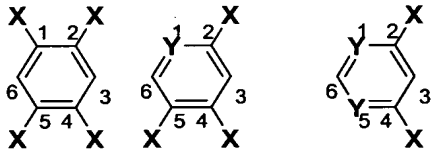
Each of **X** is independently hydrogen or a halogen, preferably a hydrogen or fluorine;



is either absent, in which case II becomes



or is selected from the group consisting of formulae **M1-M3**

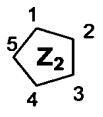


M1 , **M2** and **M3**

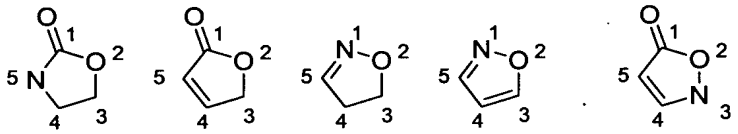
Wherein:

each **X** is defined as above;

each **Y** is independently N or CH



is selected from the group consisting of formulae **M4-M8**

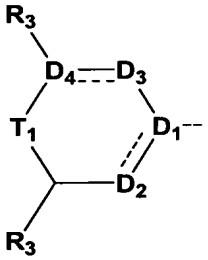


M4 , **M5** , **M6** , **M7** and **M8**

W_1 is hydroxy, halo, amino, azido, (1-4C)alkanesulfonyloxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, $NHS(O)_m$(1-4C)alkyl, $NHCOR_c$ or $NHCSR_c$; isoxazol-3-oxy, isothiazol-3-oxy, (1,2,5-thiadiazol)-3-oxy, (1,2,5-oxadiazol)-3-oxy, isoxazol-3-amino, isothiazol-3- amino, (1,2,5-thiadiazol)-3- amino, (1,2,5-oxadiazol)-3-amino, tetrazol-2-yl, tetrazol-1-yl, (1,2,3-triazol)-1-yl, (4-ethynyl-1,2,3-triazol)-1-yl, $-OL_1$, or $-N(R_c)L_2$

wherein: **m** is 0, 1, or 2; and **R_c** is H, (1-4C)alkyl, (1-4C)dihaloalkyl, (1-4C)alkoxy, methoxymethyl, acetylmethyl, methylamino or dimethylamino;

W_2 is selected from the group consisting of formulae **M9-M16**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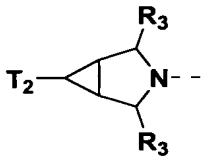
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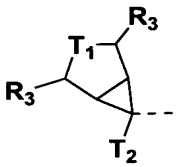
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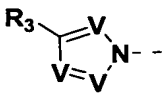
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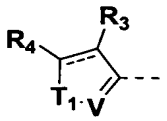
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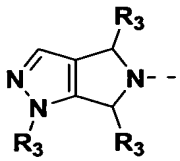
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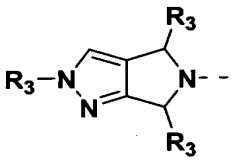
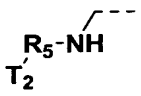

M15 and

M16

D_1, is independently CH or N and D_2, D_3 and D_4, are each independently CH, CH_2, N, S or O and each ⁼⁼⁼⁼ represents either a single bond or a double bond;

R_3 are each independently H, CH_3, CN, hydroxyl, bromo, oxo (=O), (1-4C)alkyl, (1-4C)alkylamino, (1-4C)alkoxycarbonyl, CO_2R_d, or $-OL_3$ wherein R_d is H, (1-5C)alkyl, phenyl, or heteroaryl;

T_1 is O, S, SO, SO_2, NH, NR_a, $NCOCH_2OH$, $NCOR_a$, $C(OH)CH_2N(R_a)_2$, $C(OH)CH_2OR_a$, CH-(tetrazol-2-yl), CH(tetrazol-1-yl), NL_4, $CHOL_5$, $C(OL_6)CH_2N(R_a)_2$, $C(OH)CH_2N(R_a)L_7$, $C(OL_8)CH_2OR_a$, or $C(OH)CH_2OL_9$

wherein each R_a is independently H, aryl, (1-4C)alkyl, cycloalkyl, heteroaryl, amino, (1-4C)alkylamino, or OR_b, wherein R_b is (1-6C)alkyl

T_2 is hydroxyl, amino, chloro, fluoro, bromo, $-CO_2H$, cyano, $-C(O)N(R_d)_2$, $-OL_{10}$, $-N(R_d)L_{11}$, $-N(L_{12})_2$, $-C(O)N(L_{13})_2$ or $-C(O)N(R_d)(L_{14})$ wherein each R_d is defined as above.

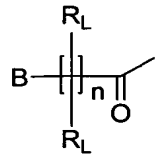
V is N or CH

R_4 is H or (1-4C) alkyl, $-(CH_2)_x-(CH(OH))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NH_2))-(CH_2)_y-Q$, , $-(CH_2)_x-(CH(OL_{15}))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NHL_{16}))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(N(L_{17})_2))-(CH_2)_y-Q$ or $-(CH_2)_x-C(O)-(CH_2)_y-Q$, wherein x and y are independently 0,1 or 2 and Q is $N(R_d)_2$, $N(R_d)L_{18}$, $N(L_{19})_2$ imidazol-1-yl, 2-methyl-imidazol-1-yl, tetrazol-2-yl or (1,2,3-triazol)-1-yl, with R_d defined as above.

R_5 is one of either $-C_mH_n$, $-(CH_2)_m-(CH(OH))-(CH_2)_b-$, $-(CH_2)_m-(CH(NH_2))-(CH_2)_b-$, $-(CH_2)_m-(CH(OH))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(NH_2))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(OL_{20}))-(CH_2)_b-$, $-(CH_2)_m-(CH(NHL_{21}))-(CH_2)_b-$, $-(CH_2)_m-(CH(N(L_{22})_2))-(CH_2)_b-$, $-(CH_2)_m-(CH(OL_{23}))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(NHL_{24}))-(CH_2)_b-C(O)-$, or $-(CH_2)_m-$

$(CH(N(L_{25})_2))$-$(CH_2)_b$-C(O)-, wherein m is an integer ≥0 and ≤10, n is an integer and ≥0 and ≤2m and b is 0,1 or 2.

Each L_1, L_3, L_5, L_6, L_8, L_9, L_{10}, L_{15}, L_{20}, and L_{23} is a linker independently selected from the group of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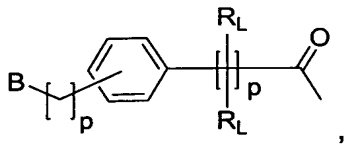
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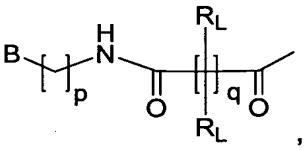
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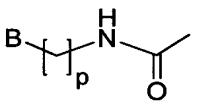
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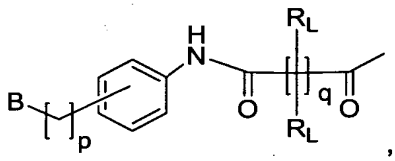
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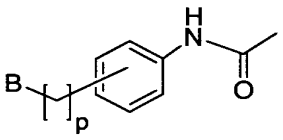
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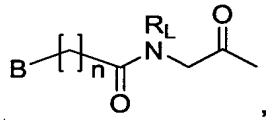
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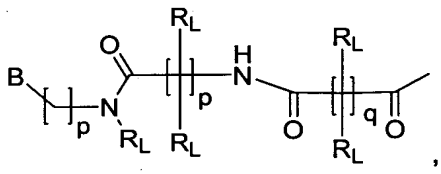
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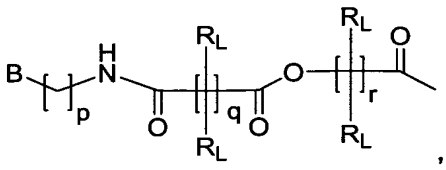
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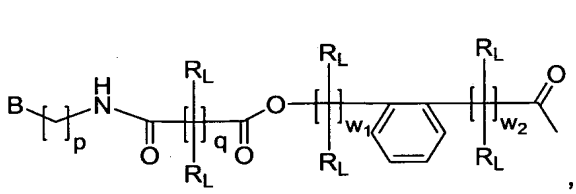
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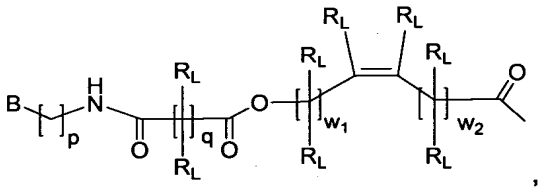
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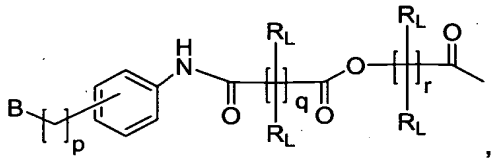
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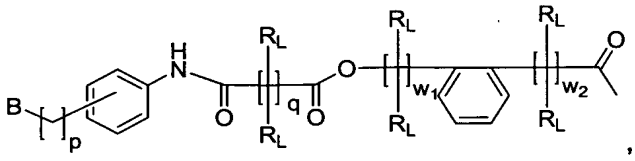
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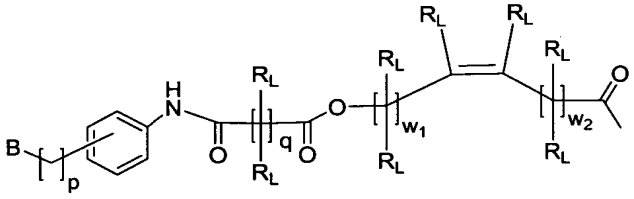
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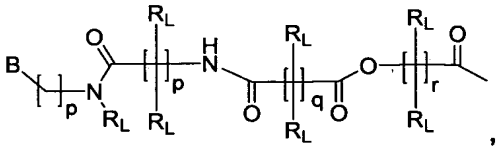
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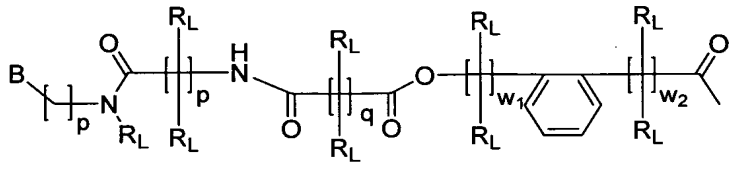
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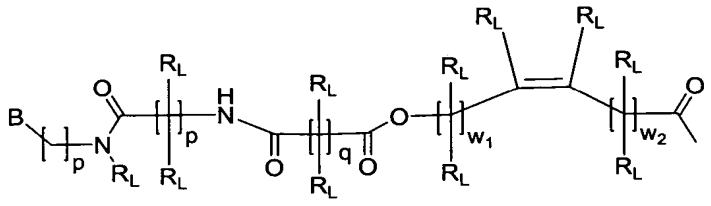


wherein:

B represents said phosphonated group;

each **p** is independently 0 or an integer ≤ 10;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl;

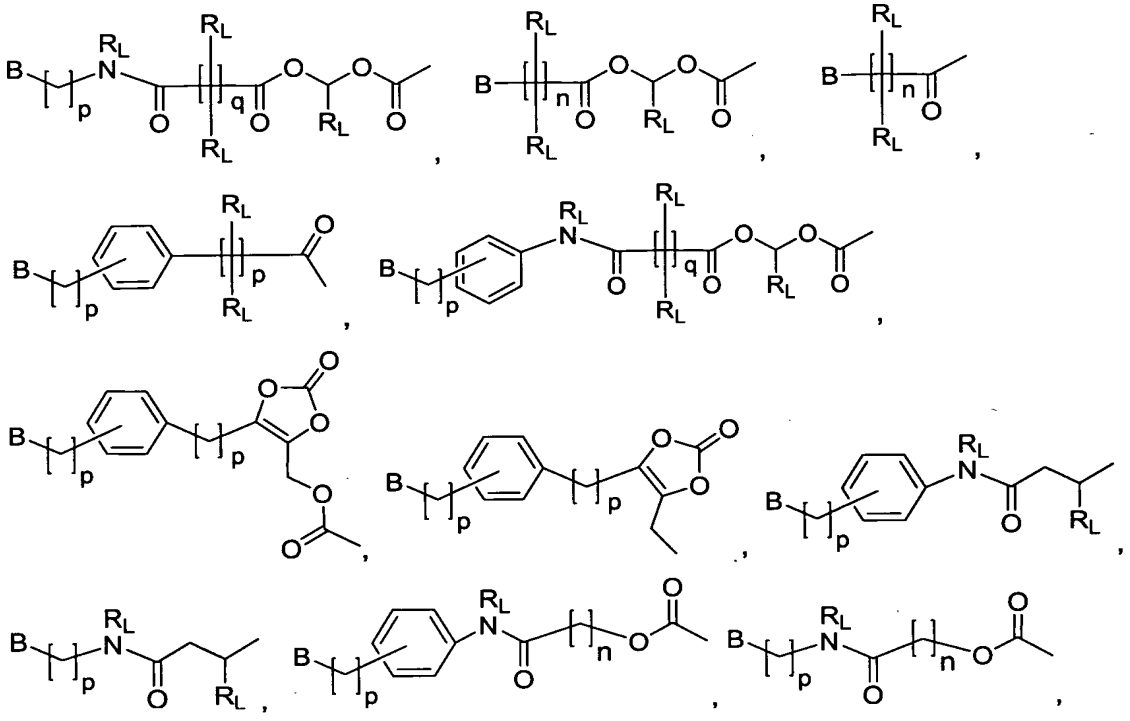
q is 2 or 3;

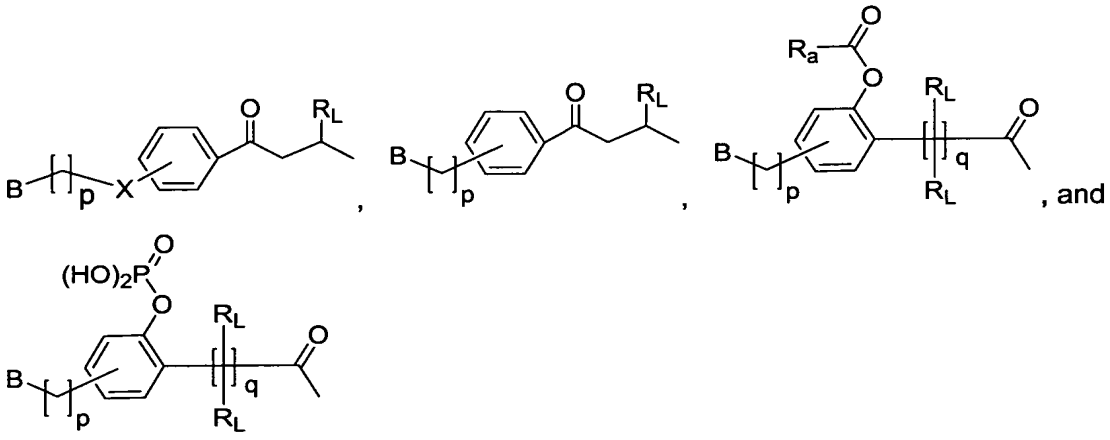
n is an integer ≤ 10;

r is 1, 2, 3, 4 or 5; and

$\mathbf{w_1}$ and $\mathbf{w_2}$ are each integers ≥ 0 such that their sum ($\mathbf{w_1} + \mathbf{w_2}$) is 1, 2 or 3.

Each $\mathbf{L_2}$, $\mathbf{L_4}$, $\mathbf{L_7}$, $\mathbf{L_{11}}$, $\mathbf{L_{12}}$, $\mathbf{L_{13}}$, $\mathbf{L_{14}}$, $\mathbf{L_{16}}$, $\mathbf{L_{17}}$, $\mathbf{L_{18}}$, $\mathbf{L_{19}}$, $\mathbf{L_{21}}$, $\mathbf{L_{22}}$, $\mathbf{L_{24}}$, and $\mathbf{L_{25}}$ is a linker independently selected from the group of





wherein:

B represents said phosphonated group;

n is an integer ≤ 10;

each **p** is independently 0 or an integer ≤ 10;

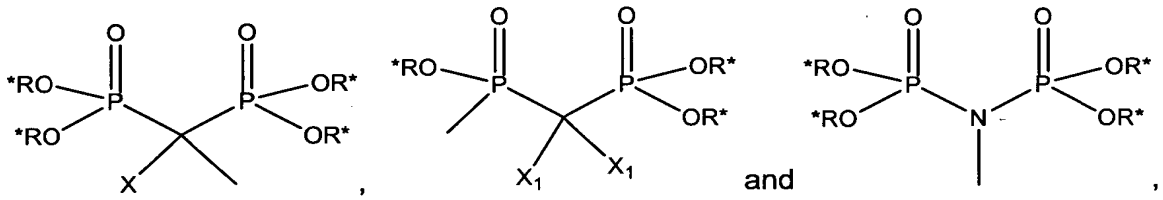
each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl;

q is 2 or 3;

X is CH_2, —CONR$_L$—, —CO—O—CH_2—, or —CO—O—; and

$\mathbf{R_a}$ is C_xH_y where x is an integer of 0 to 20 and y is an integer of 1 to 2x+1.

B is a phosphonated group selected from the group consisting of:



wherein:

each **R*** is independently selected from the group consisting of H, lower alkyl, cycloalkyl, aryl and heteroaryl, with the proviso that at least two **R*** are H;

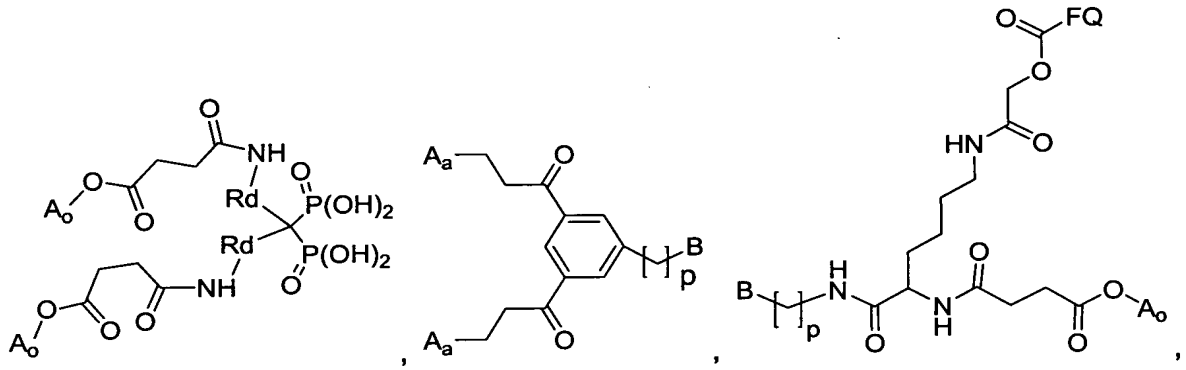
X is H, OH, NH_2, or a halo group;

each $\mathbf{X_1}$ is independently selected from the group consisting of H, OH, NH_2, and a halo group;

with the proviso that at least one of L_1, L_2, L_3, L_4, L_5, L_6, L_7, L_8, L_9, L_{10}, L_{11}, L_{12}, L_{13}, L_{14}, L_{15}, L_{16}, L_{17}, L_{18}, L_{19}, L_{20}, L_{21}, L_{22}, L_{23}, L_{24} and L_{25} is present.

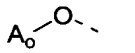
It is also conceivable according to the invention to couple a single phosphonated group to two or more antibacterial molecules. In such circumstances, the antibacterial molecules may be

the same (e.g. two molecules of Eperezolid) or different (e.g. one molecule of the fluoroquinolone antibacterial ciprofloxacin (Cipro®; US 4,670,444) and one molecule of Eperezolid). The phosphonated group may also be tethered to similar groups (e.g. the hydroxyl groups) or to different groups (e.g. the carboxyl group of one fluoroquinolone molecule and the hydroxyl group of an oxazolidinone antimicrobial molecule). Examples of potentially useful, cleavable, multi-antibacterial linkers according to the invention include, but are not limited to, those having the structures:

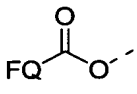


wherein: each $\mathbf{R_d}$ is independently an alkyl or an aryl group;

p is 0 or an integer ≤ 10, preferably 0, 1, 2, 3 or 4, more preferably 0 or 1;

the substructure  of the linker represents the hydroxyl moiety of the oxazolidinone antimicrobial molecule **A**;

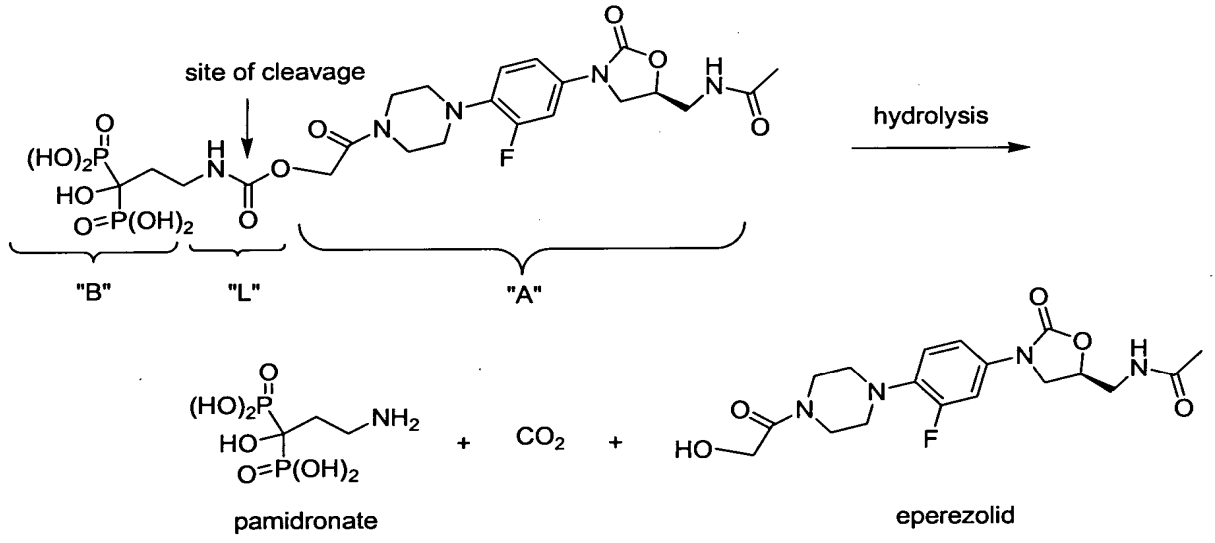
$\mathbf{A_a}$ represents an amine group of the oxazolidinone antimicrobial molecule **A**;

the substructure  of the linker represents the carboxylic moiety of a fluoroquinolone antimicrobial.

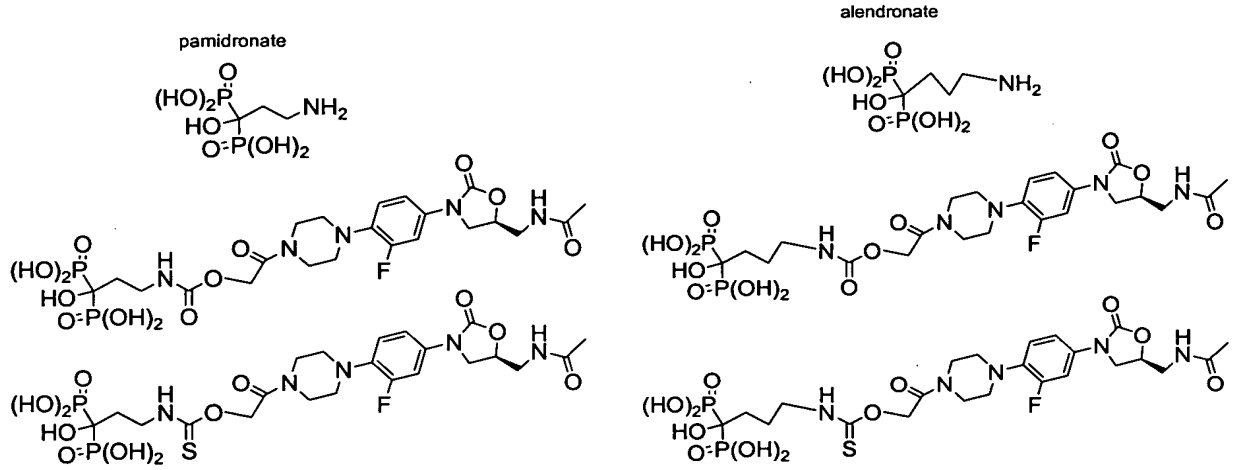
Because of its high affinity osseous tissues, the phosphonated group **B** will likely remain bond to the bones for an extended period of times (up to several years). Therefore, it is very important that the phosphonated group be endowed with low or no measurable toxicity. According to another embodiment, the phosphonated group **B** and the linker **L** are selected such that the linker is hydrolyzed or cleaved *in vivo* (preferably mostly in osseous tissues) thereby releasing: (i) the oxazolidinone antimicrobial molecule **A** and (ii) a chosen non-toxic phosphonated molecule having a proven bone therapeutic activity. Such compounds would thus have a double utility that is to: 1) provide locally to the bones for an extended period of time and/or at increased concentrations, an antibiotic useful in preventing and/or treating a bacterial

bone infection, and 2) provide to the bones a drug stimulating bone regeneration or inhibiting bone resorption, thereby facilitating bone recovery from damages caused by an infection or other injury. Suitable phosphonated molecules with proven bone therapeutic activity useful according to the invention include but are not limited to pamidronate, alendronate and incadronate as well as others such as risedronate, olpadronate, etidronate, ibandronate, zolendronate or neridronate, these molecules being well known bisphosphonate bone resorption inhibitors commonly used for the treatment of osteoporosis.

The scheme below illustrates the principles of that embodiment:



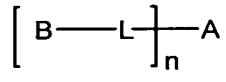
Additional specific examples of bisphosphonate derivatives according to the invention derived from pamidronate and alendronate are shown hereinafter:

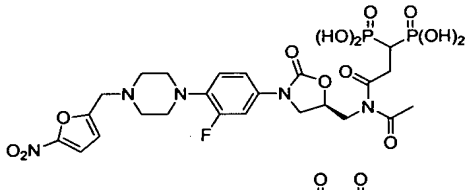


It is also conceivable according to the present invention to use a pH-sensitive linker that is cleaved only at a predetermined range of pH. In one embodiment, the pH-sensitive linker is a base-sensitive linker that is cleaved at a basic pH ranging from about 7 to about 9. According to another embodiment, the linker is an acid-sensitive linker that is cleaved at an acidic pH ranging from about 7.5 to about 4, preferably from about 6.5 and lower. It is hypothesized that such an acid-sensitive linker would allow a specific release of the oxazolidinone antibiotic mostly at a site of bacterial infection because it is known that, acidification of tissues commonly occurs during infection (O'Reilley *et al.*, Antimicrobial Agents and Chemotherapy (1992), 36(12): 2693-97).

A covalent bond or a non-cleavable linker may also covalently couple the phosphonated group **B** to the oxazolidinone **A**. Such bond or linker would be selected such that it would not be cleaved or would be cleaved mainly by the bacteria present at the actual site of infection. It is hypothesized that for such compounds the phosphonated group would remain tethered to the oxazolidinone antibiotic and the whole compound would gradually be released from the bone and absorbed by the bacteria, thereby exerting its antibacterial effect.

Of course, other types of linkers could be selected and synthesized by those skilled in the art. For instance the linker may also contain an *in vivo* hydrolysable phosphonated group having an affinity to bones as disclosed by Ilex Oncology Research in WO 04/026315. The linker may also contain an active group (e.g. a releasable group stimulating bone formation or decreasing bone resorption). These and other suitable linkers are encompassed by the present invention.

In addition to those compounds described hereinbefore and in the Exemplification section, additional compounds having the formula  according to the invention include, but are not limited to, those having the following formulae: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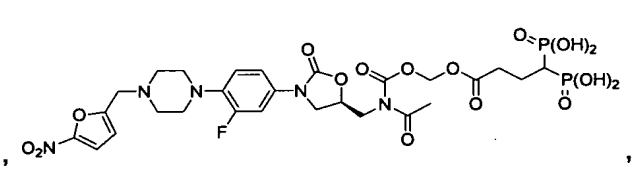
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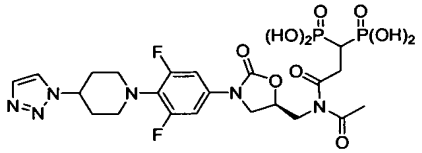
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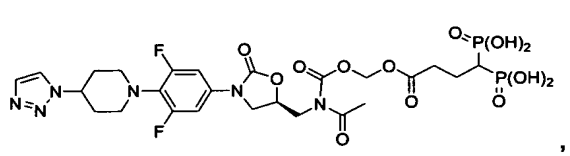
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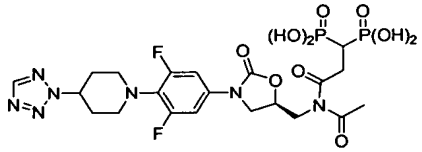
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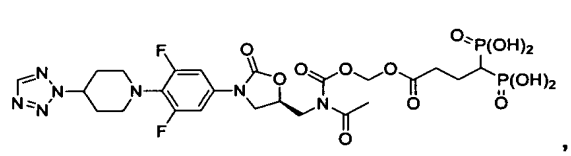
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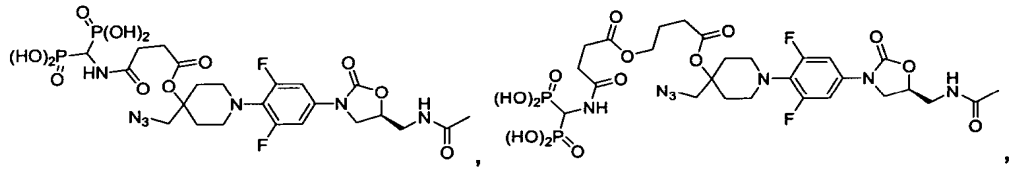
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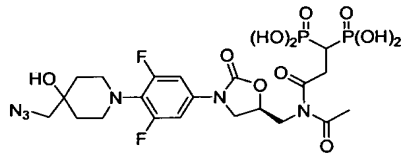
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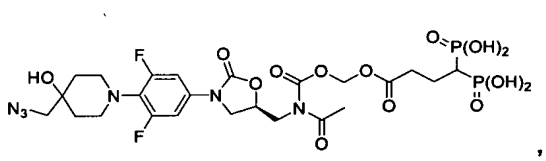
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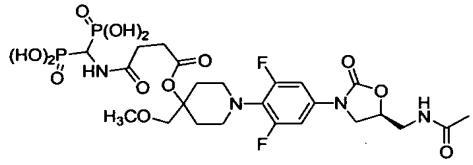
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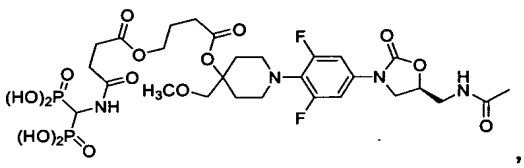
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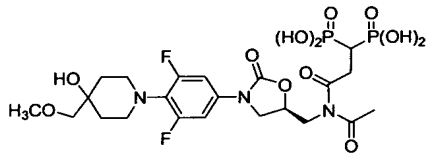
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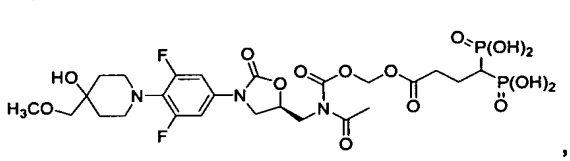
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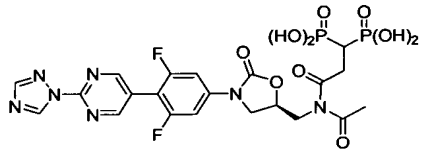
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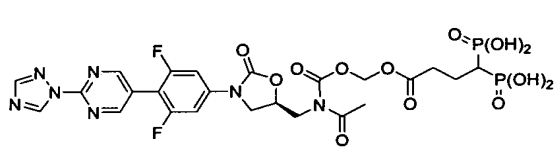
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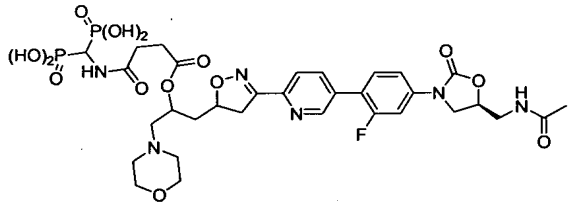
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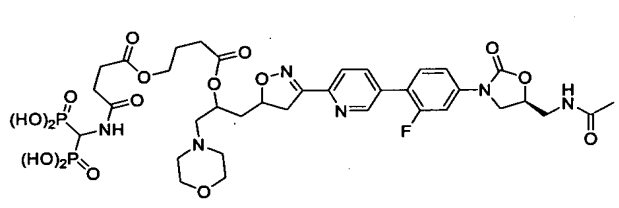
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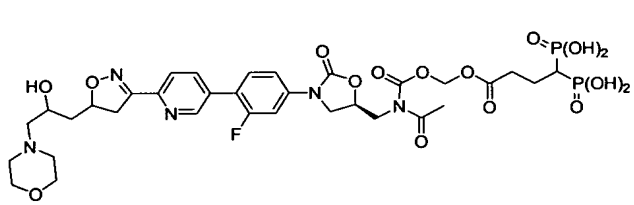
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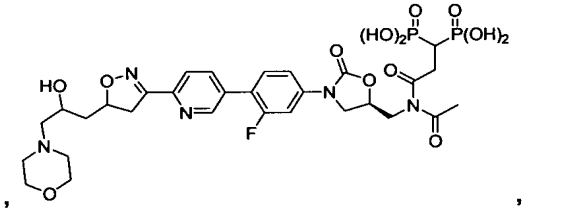
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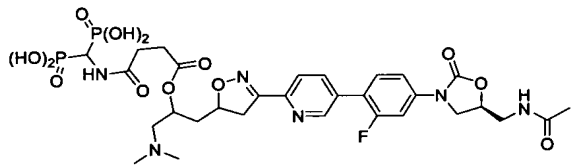
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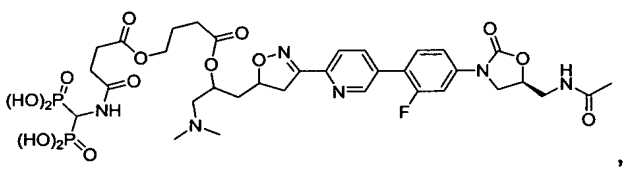
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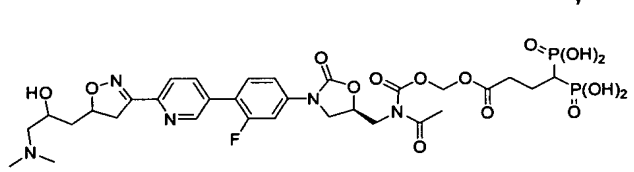
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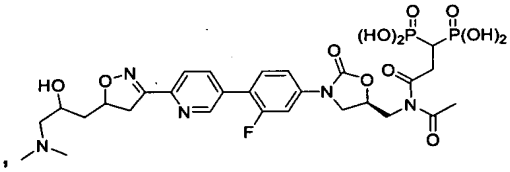
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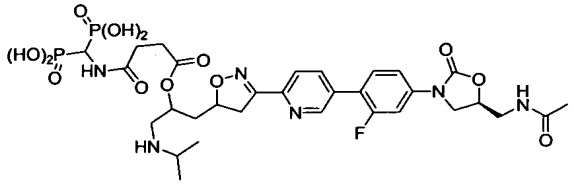
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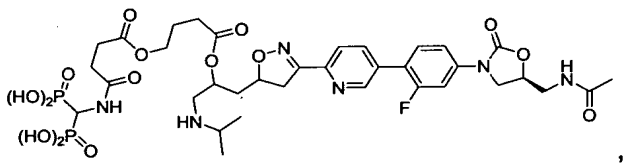
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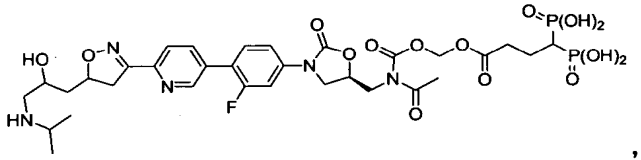
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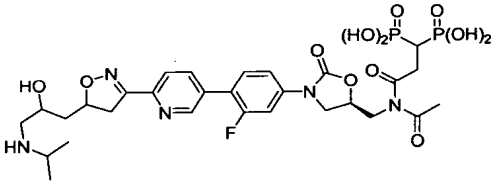
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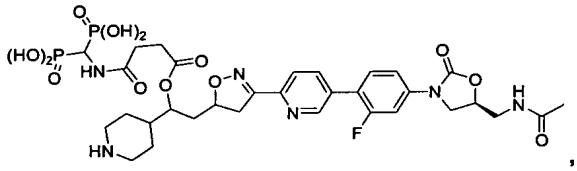
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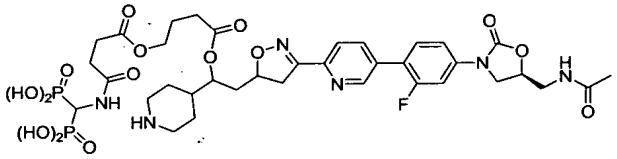
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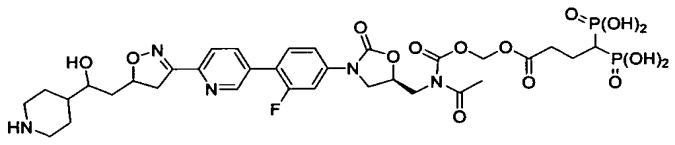
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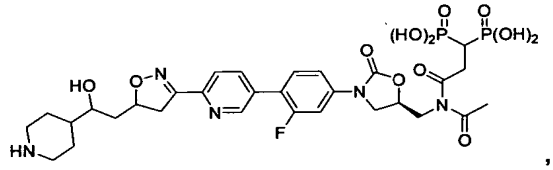
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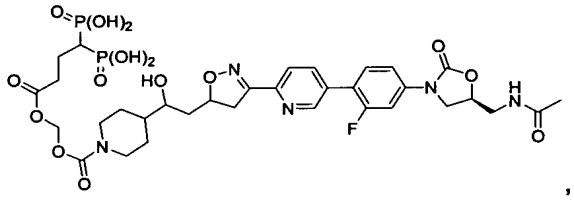
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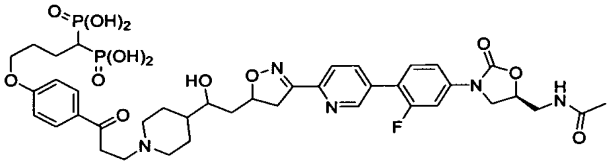
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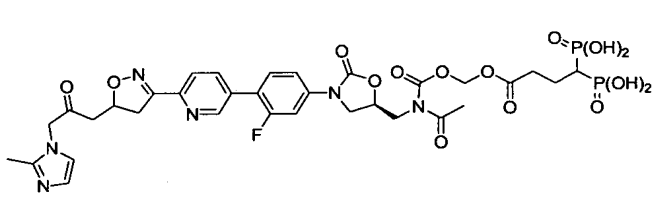
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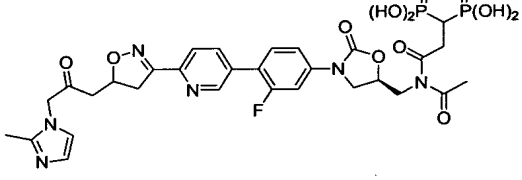
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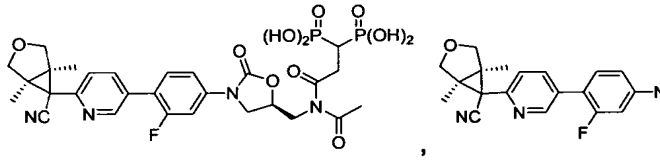
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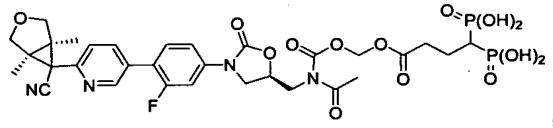
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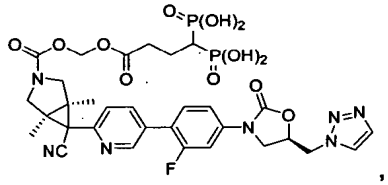
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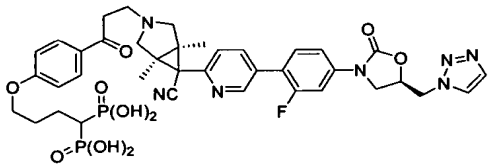
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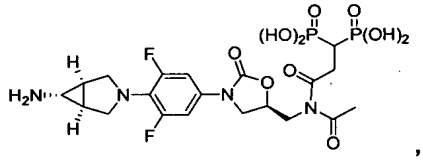
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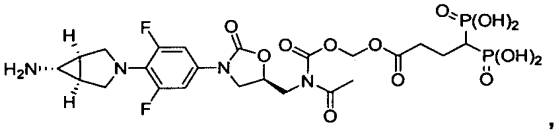
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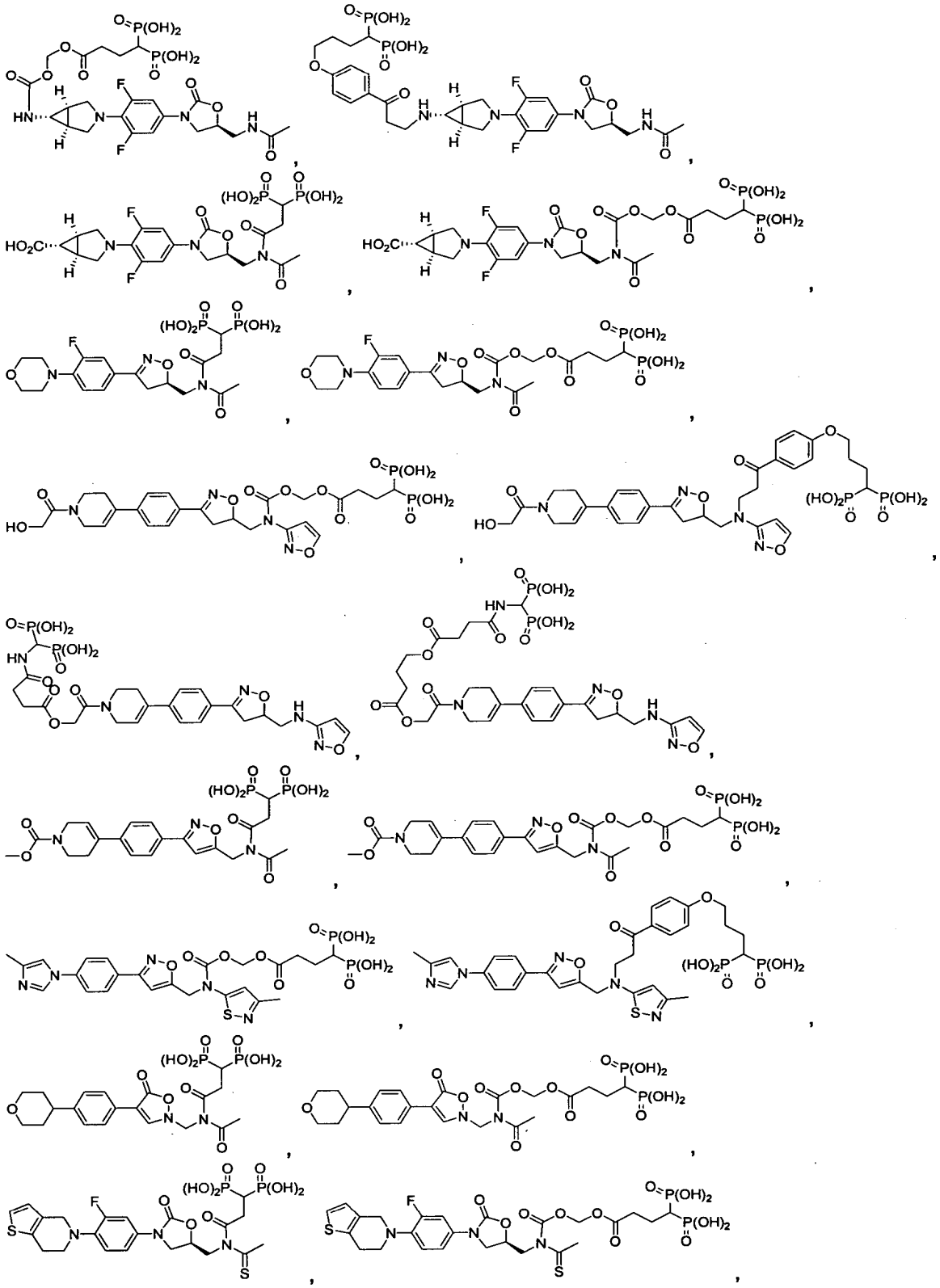

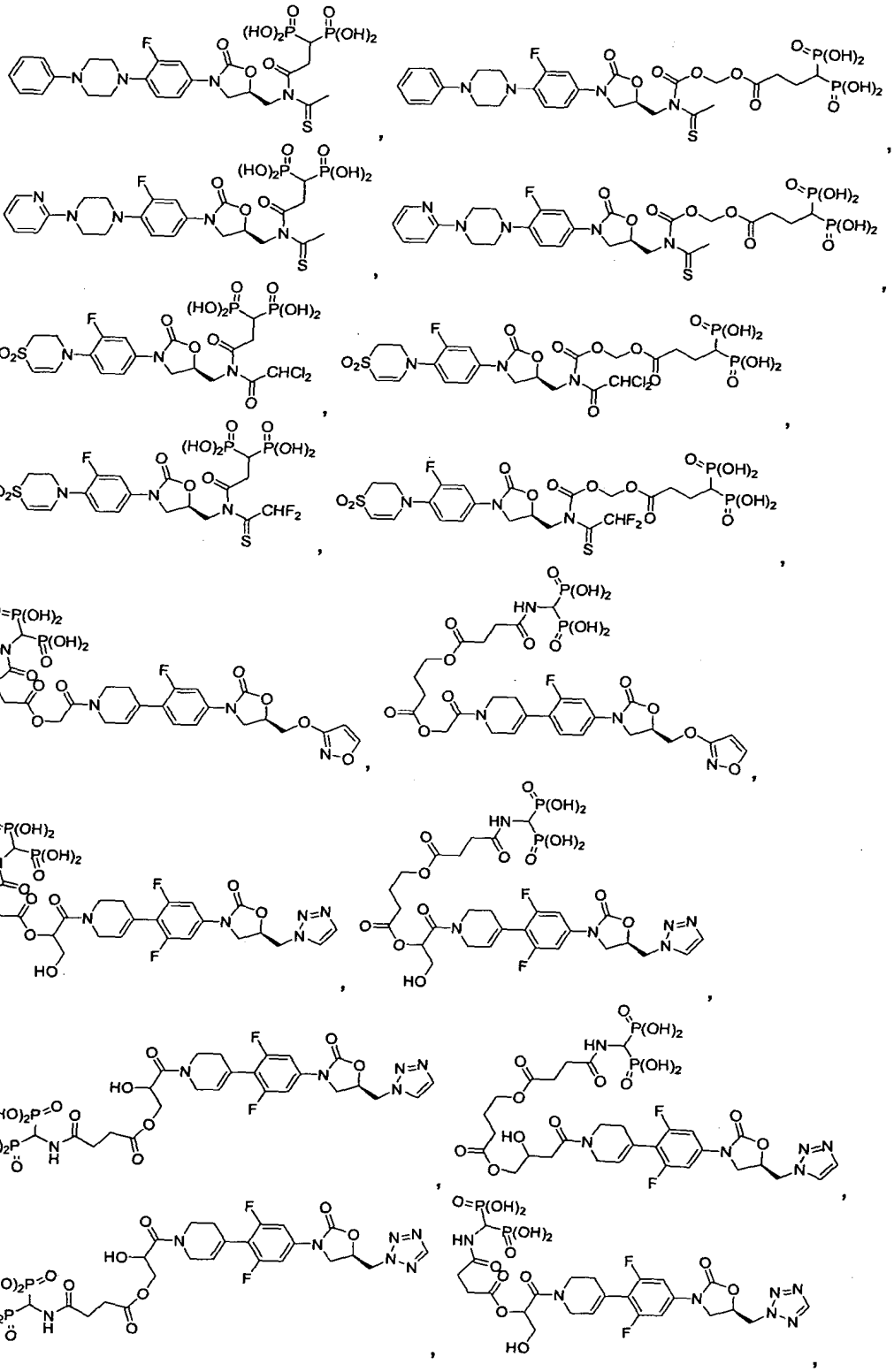

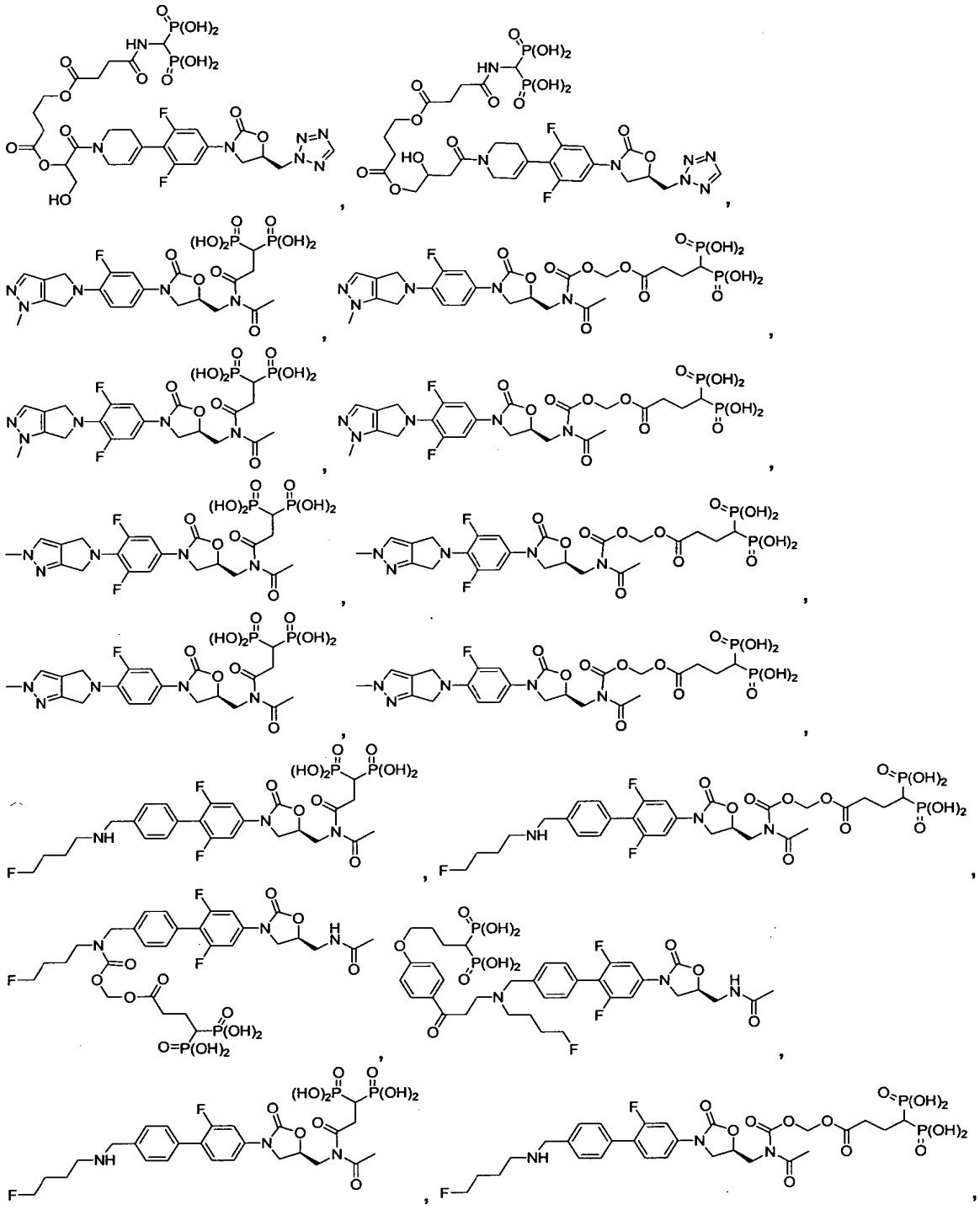

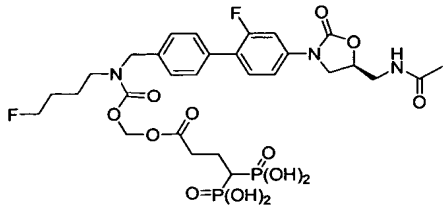
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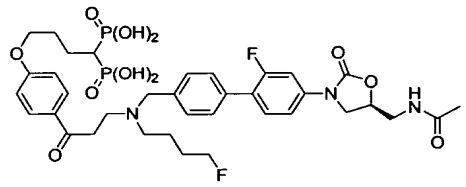
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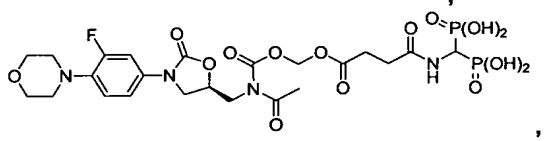
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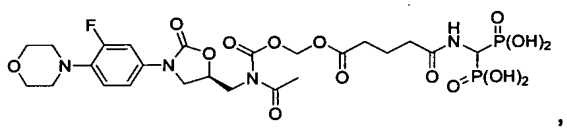
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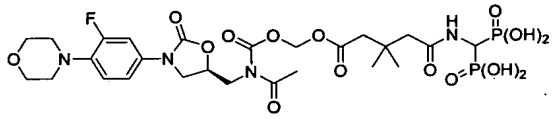
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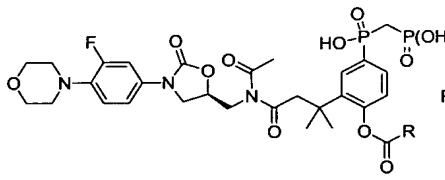
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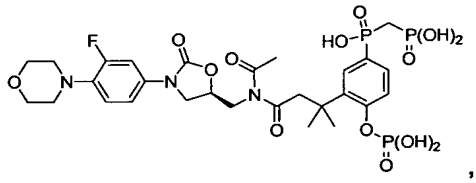
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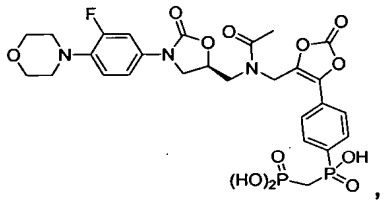
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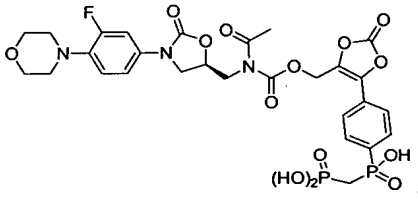
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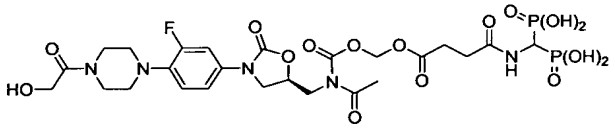
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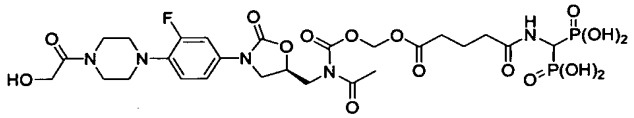
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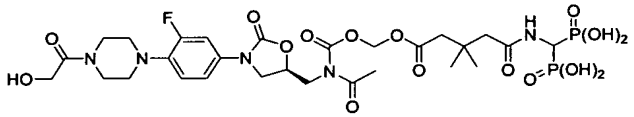
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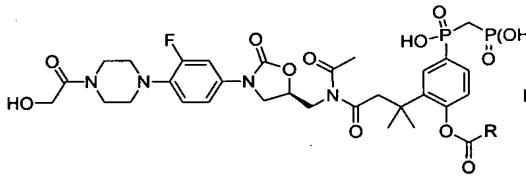
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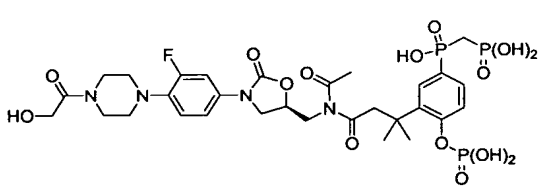
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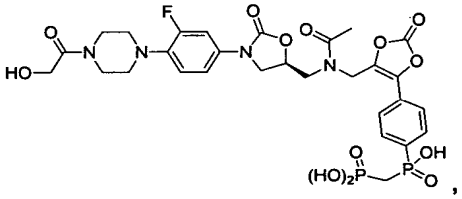
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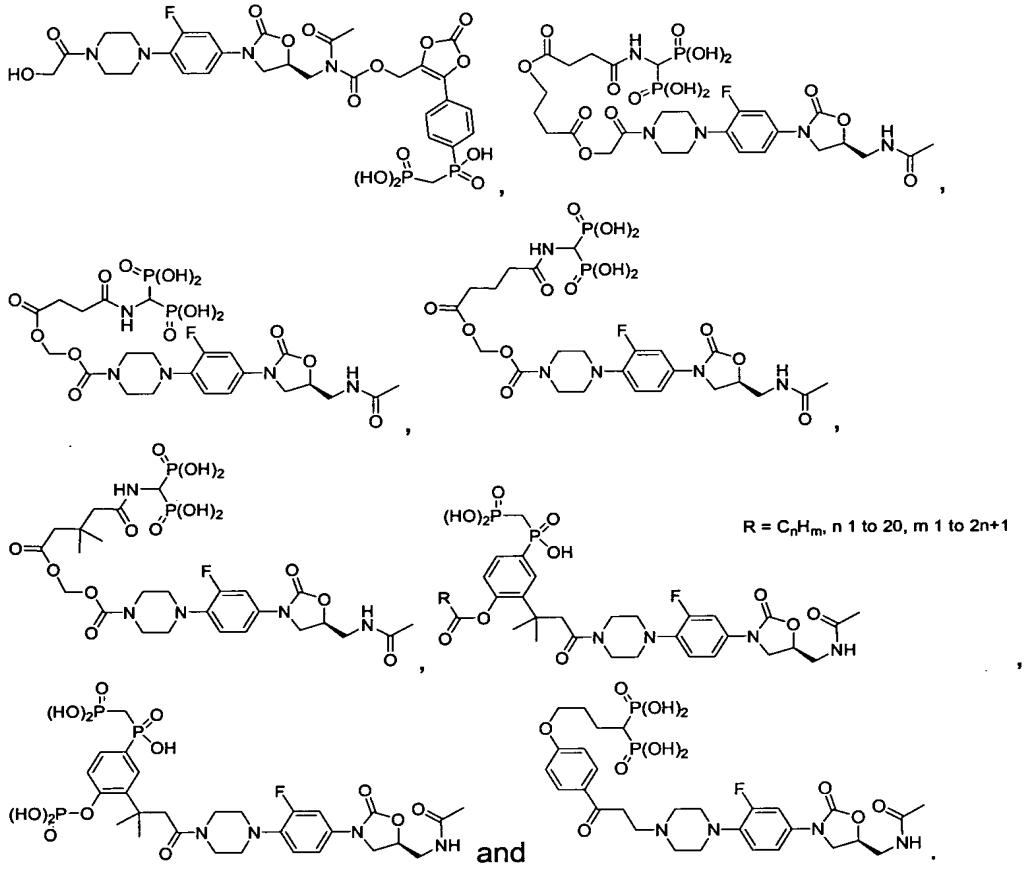

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Further, the present invention covers the compounds of Formula I and of Formula II, as well as pharmaceutically acceptable salts, esters and prodrugs thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycolates, tartrates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the inventive compound is a base, the desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid,

malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acids such as glucuronic acid and galacturonic acid, alpha-hydroxy acids such as citric acid and tartaric acid, amino acids such as aspartic acid and glutamic acid, aromatic acids such as benzoic acid and cinnamic acid, sulfonic acids such as *p*-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary), an alkali metal or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine, ammonia, primary, secondary and tertiary amines, and cyclic amines such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, and solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention.

The inventive compounds may exist as single stereoisomers, racemates and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Preferably, the inventive compounds are used in optically pure form.

It is conceivable that the compounds of the Formula I and/or of Formula II be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of the Formula I or of Formula II. Examples of prodrugs include *in vivo* hydrolysable esters of a compound of the Formula I and/or of Formula II.

An *in vivo* hydrolysable ester of a compound of the Formula I and/or of Formula II containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolyzed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the Formula I and/or of Formula II containing a hydroxy group includes inorganic esters such as phosphate esters and alpha-acyloxyalkyl ethers and related compounds which as a result of *in vivo* hydrolysis of the ester

break down to give the parent hydroxy group. Examples of alpha-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

C) Methods of preparation

The inventive compounds, and their salts, solvates, crystal forms, active metabolites, and prodrugs, may be prepared by employing the techniques available in the art using starting materials that are readily available. Certain novel and exemplary methods of preparing the inventive compounds are described in the Exemplification section. Such methods are within the scope of this invention.

D) Antimicrobial compositions and methods of treatment

A related aspect of the invention concerns the use of compounds of the invention as an active ingredient in a therapeutic or anti-bacterial composition for treatment or prevention purposes.

Pharmaceutical compositions

The compounds of the present invention may be formulated as pharmaceutically acceptable compositions.

The present invention provides for pharmaceutical compositions comprising a compound of the present invention (e.g., those compounds of Formula (I) and (II)) in combination with a pharmaceutically acceptable carrier or excipient. Preferably, the compound of the present invention is a therapeutically effective amount of the compound. Such carriers include, but are not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof.

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions according to the invention are known to those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for various routes of administration.

The compounds and compositions of the invention are conceived to have a broad spectrum of activity, including antibiotic resistant strains, against both Gram-positive (e.g. *Staphylococcus aureus, Staphylococcus epidermis, Streptococcus pyogenes, Enterococcus faecalis)* and Gram-negative bacteria (e.g. *E. coli, Chlamydia pneumoniae, Enterobacter sp., H. influenza, K. pneumoniae, Legionella pneumoniae, P. aeruginosa*).

Pharmaceutical compositions and a second therapeutic agent

A wide range of second therapeutic agents, such as antibiotics, can be used in combination with the compounds, compositions and methods of the present invention. Antibiotics used as second therapeutic agents may act by interfering with cell wall synthesis, plasma membrane integrity, nucleic acid synthesis, ribosomal function, folate synthesis, etc. A non-limiting list of useful antibiotics with which the compounds and compositions might be combined includes: Rifamycins, sulfonamides, beta-lactams, tetracyclines, chloramphenicol, aminoglycosides, macrolides, glycopeptides, streptogramins, quinolones, fluoroquinolones, oxazolidinones and lipopeptides. In particular, tetracycline, tetracycline derived antibacterial agents, glycylcycline, glycylcycline derived antibacterial agents, minocycline, minocycline derived antibacterial agents, oxazolidinone antibacterial agents, aminoglycoside antibacterial agents, quinolone antibacterial agents, vancomycin, vancomycin derived antibacterial agents, teicoplanin, teicoplanin derived antibacterial agents, eremomycin, eremomycin derived antibacterial agents, chloroeremomycin, chloroeremomycin derived antibacterial agents, daptomycin, daptomycin derived antibacterial agents, rifamycin and rifamycin derived antibacterial agents are preferred.

Methods for inhibiting bacterial growth

According to a related aspect, the present invention concerns methods of inhibiting bacterial growth, and more particularly growth of Gram-positive bacteria. The method comprises contacting the bacteria for the purpose of such inhibition with an effective amount of a phosphonated oxazolidinone compound or composition according to the invention (or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof). For example, one can inhibit ribosomal-dependent protein synthesis in a Gram-positive bacterium by contacting such a bacterium with a compound of the invention.

The contacting may be carried out *in vitro* (in biochemical and/or cellular assays), *in vivo* in a non-human animal, *in vivo* in mammals, including humans and/or *ex vivo* (e.g. for sterilization purposes).

The activity of the inventive compounds as inhibitors of ribosomal-dependent protein synthesis may be measured by any of the methods available to those skilled in the art, including *in vivo* and *in vitro* assays. Some examples of suitable assays for measurement of ribosomal-dependent protein synthesis have been described by Pratt *et al.* (Journal of Biomolecular Screening 9(1), 2004), Murray *et al.* (Antimicrobial Agents and Chemotherapy, (2001), 45 (6): 1900-04), Murray *et al.* (Antimicrobial Agents and Chemotherapy, (1998), 42 (4): 947-950) and Dandliker *et al* (Antimicrobial Agents and Chemotherapy (2003), 47: 3831-3839).

A related aspect of the invention concerns the use of a compound of the invention as an active ingredient in a pharmaceutical, therapeutic or anti-bacterial composition for treatment purposes. As defined above, "treating" or "treatgment" means at least the mitigation of a disease condition associated with a bacterial infection in a subject, including mammals such as a human, that is alleviated by a reduction of growth, replication, and/or propagation of any bacterium, such as Gram-positive organisms, and includes curing, healing, inhibiting, relieving from, improving and/or alleviating, in whole or in part, the disease condition.

The pharmaceutical compositions may be administered in any effective, convenient manner including, for instance, administration by topical, parenteral, oral, anal, intravaginal, intravenous, intraperitoneal, intramuscular, intraocular, subcutaneous, intranasal, intrabronchial, or intradermal routes among others.

In therapy or as a prophylactic, the compound(s) of the invention and/or pharmaceutically acceptable prodrugs, salts, active metabolites and solvates may be administered to an individual as an injectable composition, for example as a sterile aqueous dispersion, preferably isotonic. Alternatively the composition may be formulated for topical application for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

Alternative means for systemic administration include transmucosal and transdermal administration using penetrants such as bile salts or fusidic acids or other detergents. In addition, if a compound of the present invention can be formulated in an enteric or an encapsulated formulation, oral administration may also be possible. Administration of these compounds may also be topical and/or localized, in the form of salves, pastes, gels, and the like.

While the treatment can be administered in a systemic manner through the means described above, it may also be administered in a localized manner. For example, the treatment may be administered directly to a bone, such as through an injection into a bone. The treatment may also be administered in other localized manners, such as application to a wound through a topical composition or directly into a subcutaneous or other form of wound.

The active compound(s) and its pharmaceutically acceptable prodrugs, salts, metabolites and solvates may be also administered to an individual as part of a bone substitute or bone-repair compound such as bone cements or fillers (e.g. Skelite™, Millenium Biologics, Kingston, ON, Canada) and calcium or hydroxyapatite beads.

A dose of the pharmaceutical composition contains at least a pharmaceutically- or therapeutically-effective amount of the active compound (i.e., a compound of Formula (I), of Formula (II) and/or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof), and is preferably made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment. A "therapeutically effective amount" is intended to mean that amount of a compound of Formula (I) and/or of Formula (II) (and/or a pharmaceutically acceptable prodrug, salt, active metabolite, or solvate thereof) that confers a therapeutic effect on the subject treated. The therapeutic effect may be objective (i.e. measurable by some test or marker (e.g. lower bacterial count)) or subjective (i.e. the subject gives an indication of or feels an effect).

The amount that will correspond to a "therapeutically effective amount" will vary depending upon factors such as the particular compound, the route of administration, excipient usage, the disease condition and the severity thereof, the identity of the mammal in need thereof, and the possibility of co-usage with other agents for treating a disease. Nevertheless the therapeutically effective amount can be readily determined by one of skill in the art. For administration to mammals, and particularly humans, it is expected that the daily dosage level of the active compound will be from 0.1 mg/kg to 200 mg/kg, typically around 1-5 mg/kg. The physician in any event will determine the actual dosage that will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The invention provides a method of treating a subject in need of treatment wherein a phosphonated Oxazolidinone antimicrobial molecule having high affinity to osseous tissues is administered to the subject. Preferably, the phosphonated group is coupled to the Oxazolidinone antimicrobial molecule through a cleavable linker. Preferably the subject is a mammal, such as a human. The method of treatment may also be applied in a veterinary

aspect, to animals such as farm animals including horses, cattle, sheep, and goats, and pets such as dogs, cats and birds.

Although the invention is preferably directed to the prevention and/or treatment of bone-related infections, the invention encompasses therapeutic and prophylactic methods against other diseases caused by or related to bacterial infection, including but not limited to otitis, conjunctivitis, pneumonia, bacteremia, sinusitis, pleural emphysema and endocarditis, low grade infections in the vicinity of calcifications of atherosclerotic vessels, and meningitis. In such methods, an effective therapeutic or prophylactic amount of an antibacterial compound and/or composition as defined hereinbefore, is administered to a mammal (preferably a human) in an amount sufficient to provide a therapeutic effect and thereby prevent or treat the infection of the mammal. Exact amounts can be routinely determined by one skilled in the art and will vary depending on several factors, such as the particular bacterial strain involved and the particular antibacterial compound used.

Prophylaxis and prevention

An additional use that is particularly contemplated for the compounds invention is for prophylaxis and prevention purposes. Indeed, many orthopedic surgeons consider that humans with prosthetic joints should be considered for antibiotic prophylaxis before a treatment that could produce a bacteremia. Deep infection is a serious complication sometimes leading to loss of the prosthetic joint and is accompanied by significant morbidity and mortality. The compounds and compositions of the invention may therefore be used as a replacement for prophylactic antibiotics in this situation. For instance, the compounds and/or compositions of the invention may be administered by injection to achieve a systemic and/or local effect against relevant bacteria shortly before an invasive medical treatment, such as surgery or insertion of an in-dwelling device (e.g. joint replacement (hip, knee, shoulder, etc.), bone grafting, fracture repair, dental operation or implant. Treatment may be continued after invasive medical treatment, such as post-operatively or during the in-body time of the device.

In addition, the compound and/or composition may also be administered before the invasive medical treatment to permit the accumulation of the compound into the bone tissues prior to the treatment.

In each instance, the compound(s) of the invention could be administered once, twice, thrice or more, from 1, 2, 3, 4, 5, 6, 7 days or more, to 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 hour or less before surgery for permitting an advisable systemic or local presence of the compounds, and/or accumulation in the bones, preferably in the areas potentially exposed to bacterial contamination during the surgical procedure. Even more preferably, the phosphonated compounds of the

invention would be administered such that they can reach a local concentration of about 5, 10, 20, 30, 40, 50, 75, 100, 500 or even 1000 fold higher concentration than the concentration that would normally be achieved during the administration of the unmodified parent Oxazolidinone antimicrobial molecule, i.e. a non-phosphonated equivalent. The compound(s) may be administered after the invasive medical treatment for a period of time, such as 1, 2, 3, 4, 5 or 6 days, 1, 2, 3 or more weeks, or for the entire time in which the device is present in the body.

Therefore, the invention provides a method of inducing accumulation of an oxazolidinone antimicrobial molecule in bones of a mammal wherein a phosphonated Oxazolidinone antimicrobial molecule having high affinity to osseous tissues is administered to a mammal. The phosphonated Oxazolidinone antimicrobial molecule binds osseous tissues and accumulates in bones of the mammal in amounts greater than amounts of a non-phosphonated equivalent of the Oxazolidinone antimicrobial molecule. Preferably, the phosphonated group is coupled to the Oxazolidinone antimicrobial molecule through a cleavable linker.

The invention further provides a method for prolonging the presence of an oxazolidinone antimicrobial molecule in bones of a mammal wherein a phosphonated Oxazolidinone antimicrobial molecule having a high affinity to osseous tissues is administered to a mammal. The phosphonated group is coupled to the Oxazolidinone antimicrobial molecule through a cleavable linker. The phosphonated Oxazolidinone antimicrobial molecule binds osseous tissues and accumulates in bones of the mammal, and the linker is cleaved gradually within the bones thereby releasing the Oxazolidinone antimicrobial molecule and prolonging the presence of the Oxazolidinone antimicrobial molecule in the bones.

E) In-dwelling devices and products coated with the phosphonated Oxazolidinone antimicrobial molecules of the invention

The invention further encompasses in-dwelling devices coated with the compounds of the invention. As used herein, the term "in-dwelling device" refers to surgical implants, orthopedic devices, prosthetic devices and catheters, i.e., devices that are introduced to the body of an individual and remain in position for an extended time. Such devices include, but are not limited to, artificial joints and implants, heart valves, pacemakers, vascular grafts, vascular catheters, cerebrospinal fluid shunts, urinary catheters, continuous ambulatory peritoneal dialysis (CAPD) catheters.

According to one embodiment, the in-dwelling device is bathed in or sprayed with a concentration of about 1 mg/ml to about 10 mg/ml of the compound and/or the composition of the invention, before its insertion in the body.

According to another embodiment, the in-dwelling device is made of, or pre-coated with, an osseous-like type of material (e.g. calcium phosphate, Ca-ion and hydroxyapatite (Yoshinari et al., Biomaterials (2001), 22(7): 709-715)). Such material is likely to advantageously improve binding of the compounds of the invention to the in-dwelling device, either during the coating of the device with the compounds of the invention and/or after their local or systemic administration. The in-dwelling devices may also be coated with an osseous material pre-loaded with or containing bound bone-targeting compound(s) according to the invention. For the above-mentioned embodiments, hydroxyapatite would be preferred as the osseous material. More details on coating methods, uses and advantages of hydroxyapatite-coated prostheses are found in the review by Dumbleton and Manly (The Journal of Bone & Joint Surgery (2004) 86A:2526-40) which is incorporated herein by reference.

F) Methods of preparation

The inventive compounds, and their salts, solvates, crystal forms, active metabolites, and prodrugs, may be prepared by employing the techniques available in the art using starting materials that are readily available. Certain novel and exemplary methods of preparing the inventive compounds are described in the Exemplification section below. Such methods are within the scope of this invention.

EXAMPLES

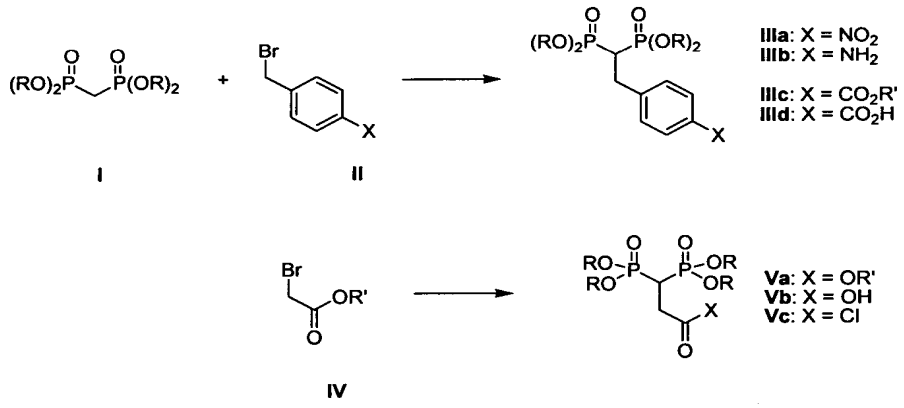
The Examples set forth herein below provide exemplary syntheses of certain representative compounds of the invention. Also provided are exemplary methods for assaying the compounds of the invention for their activity as inhibitors of protein synthesis, assays for determining the minimum inhibitory concentration (MIC) of the compounds of the invention against microorganisms, and methods for testing *in vivo* activity and cytotoxicity.

Example 1: Synthesis of linezolid, eperezolid amine and eperezolid bisphosphonate conjugates

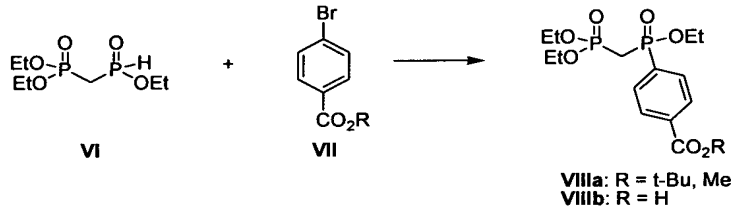
A) General Experimental Procedures

Linezolid and eperezolid and their intermediates, including eperezolid amine, can be prepared following the protocols described in *J. Med. Chem.* **1996**, *39*, 673-679.

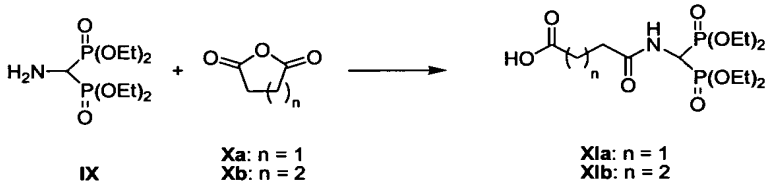
A-1) Preparation of bisphosphonate building blocks



Following protocols described in *Bioorg. Med. Chem.* **1999**, *7*, 901-919, benzyl substituted bisphosphonate building blocks of the general structures **III** and **V** can be obtained by alkylation of the anion of **I** with 4-substituted benzyl bromide **II** or bromoacetate **IV**. Nitro compound **IIIa** can be converted to aniline **IIIb** by reduction of the nitro group under hydrogenation conditions, using a catalyst such as PtO_2. Esters like **IIIc** and **Va** can be converted to the corresponding acids **IIId** or **Vb** via ester cleavage. For example, ester **IIIc** where R' = *t*-Bu can be treated with TFA to afford the corresponding acid **IIId**. Under similar conditions, ester **Va** where X = O*t*-Bu can be converted to acid **Vb**.

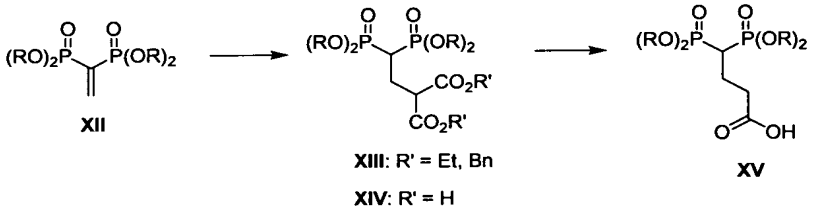


Diethyl (ethoxyphosphinyl)methylphosphonate **VI** can be prepared using the procedure described in *Synth. Comm.* **2002**, *32*, 2951-2957 and patent US 5,952,478 (1999). It can be coupled with a 4-substituted bromobenzene (**VII**) to access acid **VIIIb**, following cleavage of the ester intermediate **VIIIa**.

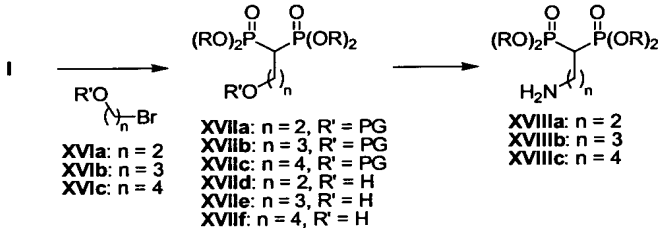


Amine **IX** can be prepared from dibenzylamine, diethyl phosphite and triethyl orthoformate following a protocol described in *Synth. Comm.* **1996**, *26*, 2037-2043. Acylation of

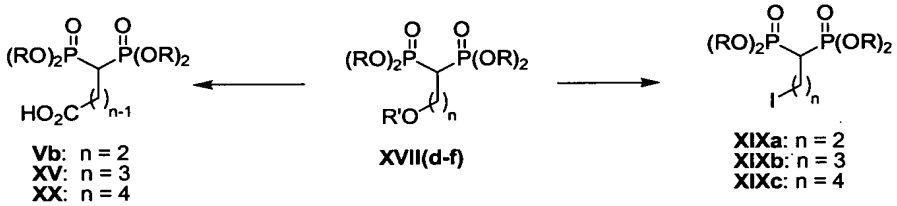
IX with succinic anhydride **Xa** or glutaric anhydride **Xb** can provide acids **XIa** and **XIb** respectively (*J. Drug Targeting* **1997**, *5*, 129-138).



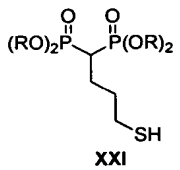
Olefin **XII** can be prepared from **I** following a protocol described in *J. Org. Chem.* **1986**, *51*, 3488-3490. It can also be converted to acid **XV** via malonate **XIII** using conditions described in *Tetrahedron* **2001**, *57*, 1837-1847.



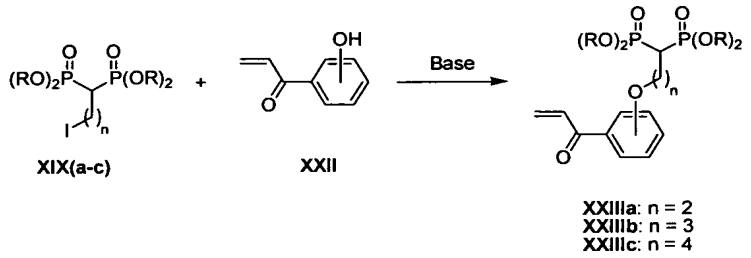
As described in *Phosphorus, Sulfur and Silicon*, **1998**, *132*, 219-229, alcohols of general structure **XVII(a-f)** and amines of general structure **XVIII(a-c)** can be prepared by alkylation of the anion of **I** by protected ω-hydroxy bromides of various chain length **XVI(a-c)**. After deprotection, alcohols can be converted to the corresponding amines via a sequence of mesylation, displacement with azide anion and reduction of the azide.



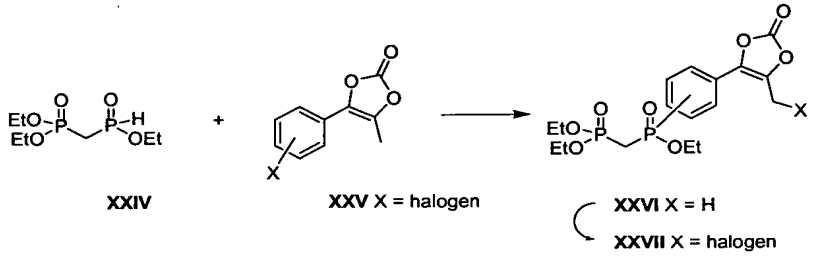
Alcohols **XVII(d-f)** can also be converted to the corresponding iodides **XIX(a-c)** via treatment with in situ generated triphenylphosphine:iodine complex. These alcohols may additionally be converted to acids of general structure **Vb**, **XV** and **XX** by conventional methods of oxidation, such as treatment with pyridinium dichromate.



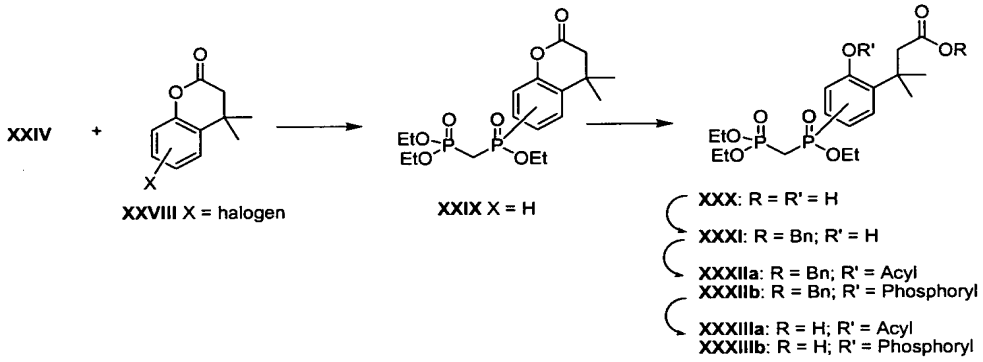
Thiol **XXI** can be prepared by alkylation of the anion of **I** with a protected 3-iodopropane-1-thiol following the protocol described in *Bioorg. Med. Chem.* **1999**, *7*, 901-919.



Vinyl ketones such as **XXIII(a-c)** can be prepared through the condensation of the parent (hydroxyphenyl) vinyl ketone **XXII** with iodides **XIX(a-c)** in the presence of an appropriately chosen base.



Diethyl (ethoxyphosphinyl)methylphosphonate **XXIV** can be prepared using the procedure described in Synth. Comm. (2002), 32: 2951-2957 and patent US 5,952,478 (1999). It can be coupled with a halogenated 1,3-dioxolone **XXV** to furnish bisphosphonate **XXVI**. This can be followed by a radical halogenation reaction to provide bisphosphonate **XXVII**.

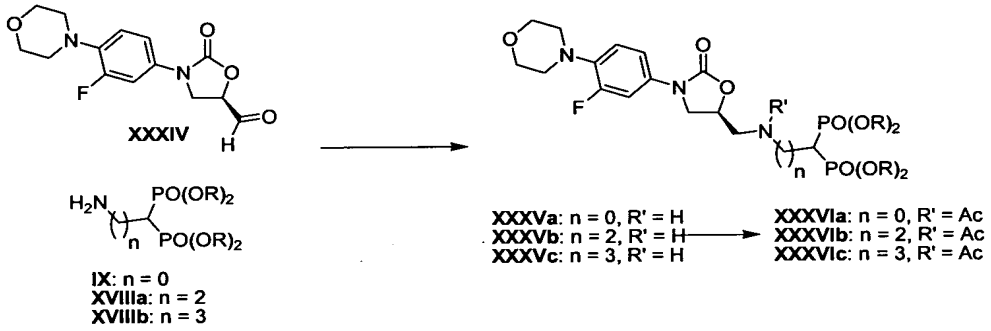


Similarly, the bisphosphonated hydrocinnamic acids **XXXIII(a-b)** can be obtained via a sequence of protections and deprotections from the bisphosphonated dihydrochromenone

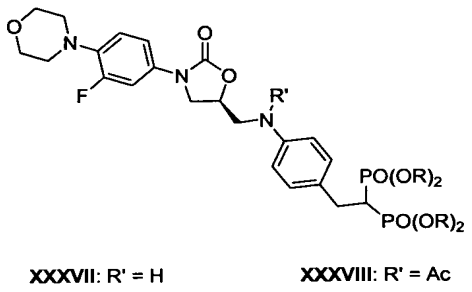
XXXIX, itself the product of a coupling between diethyl (ethoxyphosphinyl)methylphosphonate **XXIV** and halogenated dihydrochromenone **XXVIII**.

The bisphosphonate building blocks described in this section are in the form of their phosphonic esters, R being Me, Et, *i*-Pr, Allyl or Bn; or in the form of free bisphosphonic acids and/or free bisphosphonated salts.

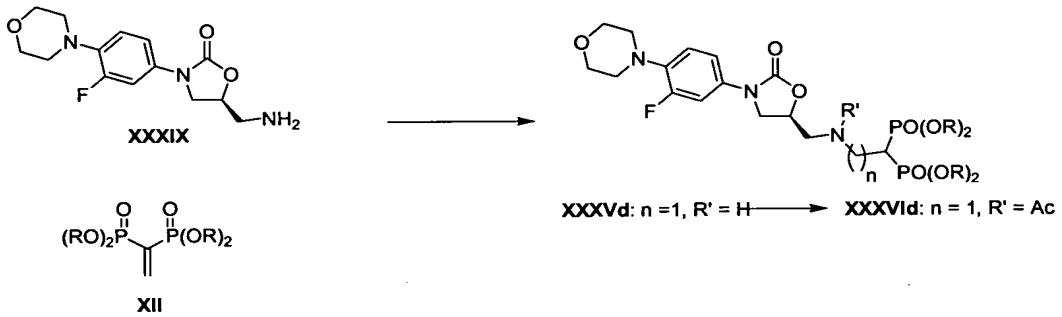
A-2) Synthesis of linezolid- and eperezolid-bisphosphonate conjugates



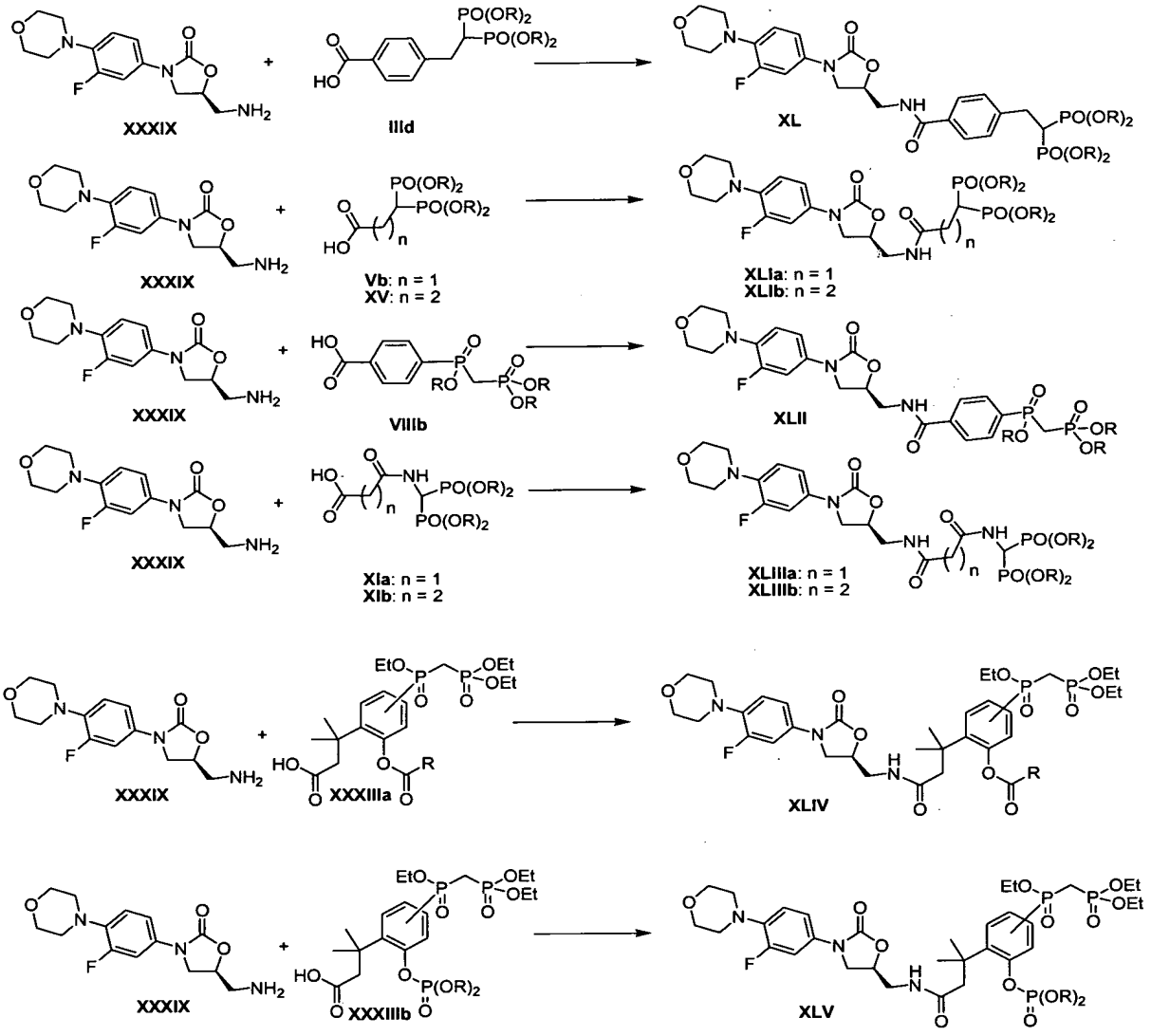
Aldehyde **XXXIV**, obtained from oxidation of the alcohol intermediate in the synthesis of linezolid, can be condensed with amines **IX**, **XVIIIa** and **XVIIIb** under conditions of reductive amination. Subsequently, amines **XXXV(a-c)** can be acetylated to provide amides **XXXVI(a-c)**.



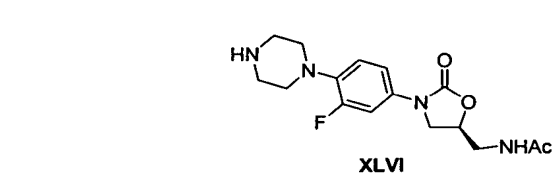
Similarly, compound **XXXVII** can be obtained from the aldehyde **XXXIV** and aniline **IIIb** and converted to amide **XXXVIII**.



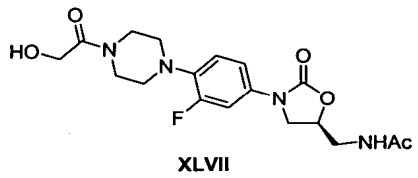
Addition of amine **XXXIX**, a key intermediate in the preparation of linezolid, to olefin **XII** can give access to adduct **XXXVd**, which can be converted to amide **XXXVId** by acetylation.



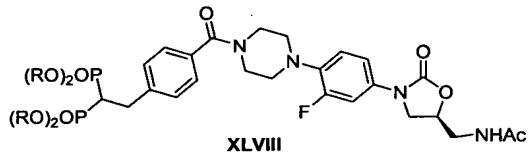
Compounds **XL** through **XLV**can be prepared by coupling the same amine **XXXIX**with the appropriate acid using a coupling agent, such as BOPCl, under typical coupling conditions. Alternatively, acids can be converted to the corresponding acid chlorides by treating the acid with $SOCl_2$ or oxalyl chloride. These acid chlorides can as the acylating agent in the conversion of amine **XXXIX**, providing amides **XL** through **XLV**.



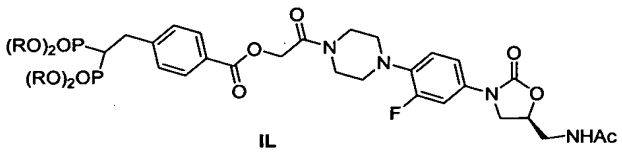
XLVI



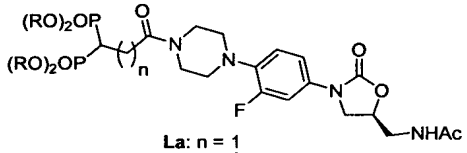
XLVII



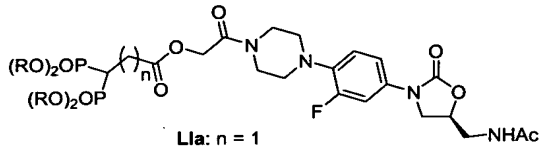
XLVIII



IL



La: n = 1
Lb: n = 2



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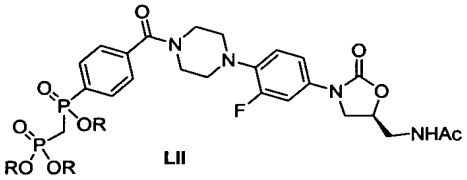
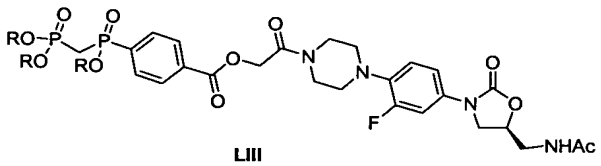
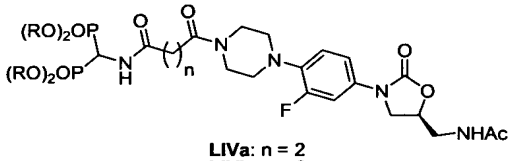


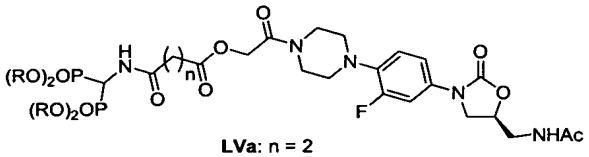
LII



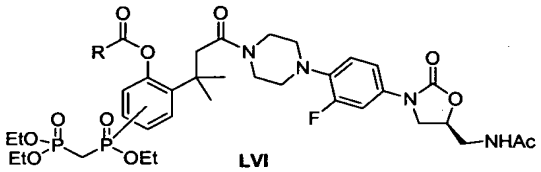
LIII



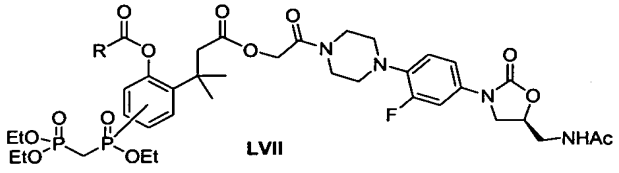
LIVa: n = 2
LIVb: n = 3



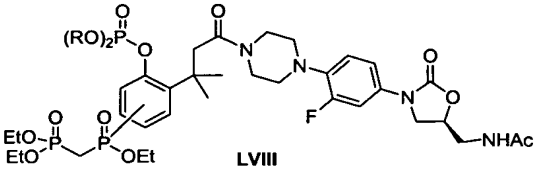
LVa: n = 2
LVb: n = 3



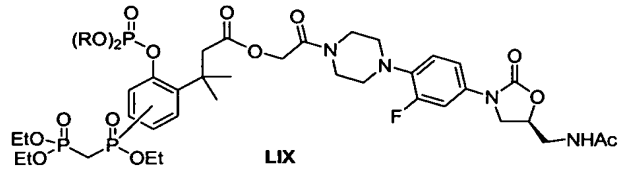
LVI



LVII



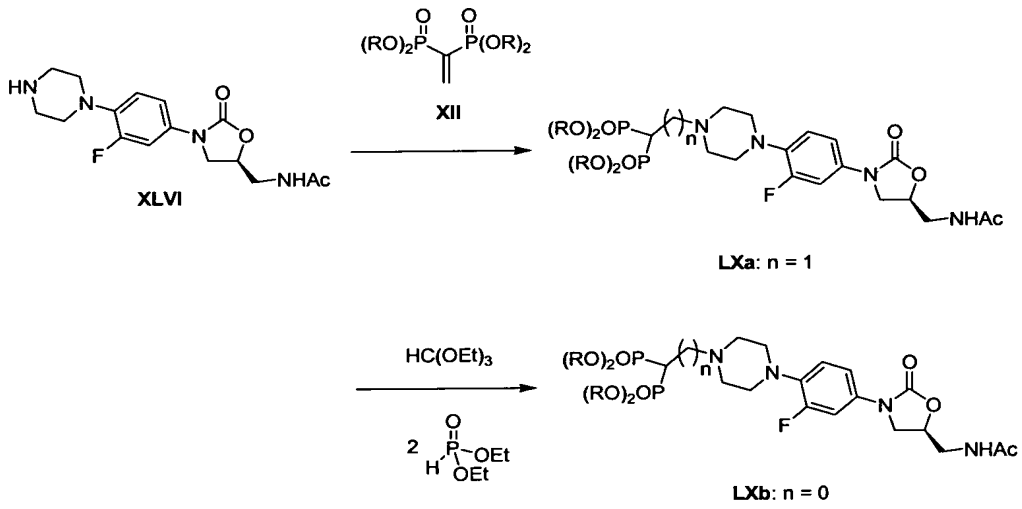
LVIII



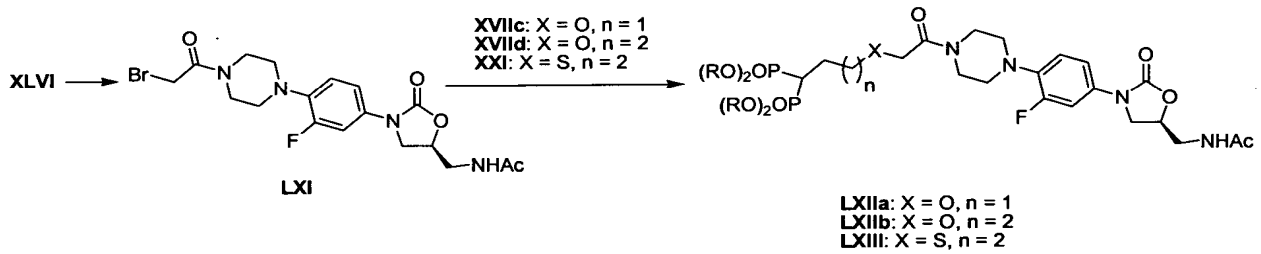
LIX

Eperezolid (**XLVII**) and its amine precursor **XLVI** can be converted into bisphosphonate conjugates **XLVIII** through **LIX** by coupling with acids **IIId, Vb, XV, VIIIb, XI(a-b)** and **XXXIII(a-b)** following a protocol similar to the one for linezolid derivatives above. Acid chlorides derived from

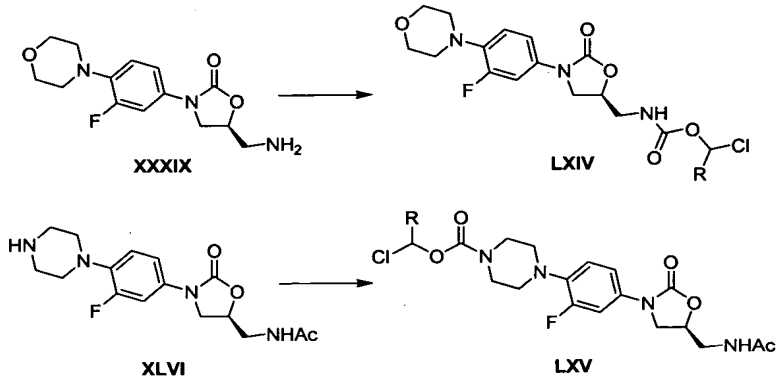
IIId, Vb, XV, VIIIb, XI(a-b) and **XXXIII(a-b)** can also be employed for this acylation to provide the same bisphosphonate conjugates.



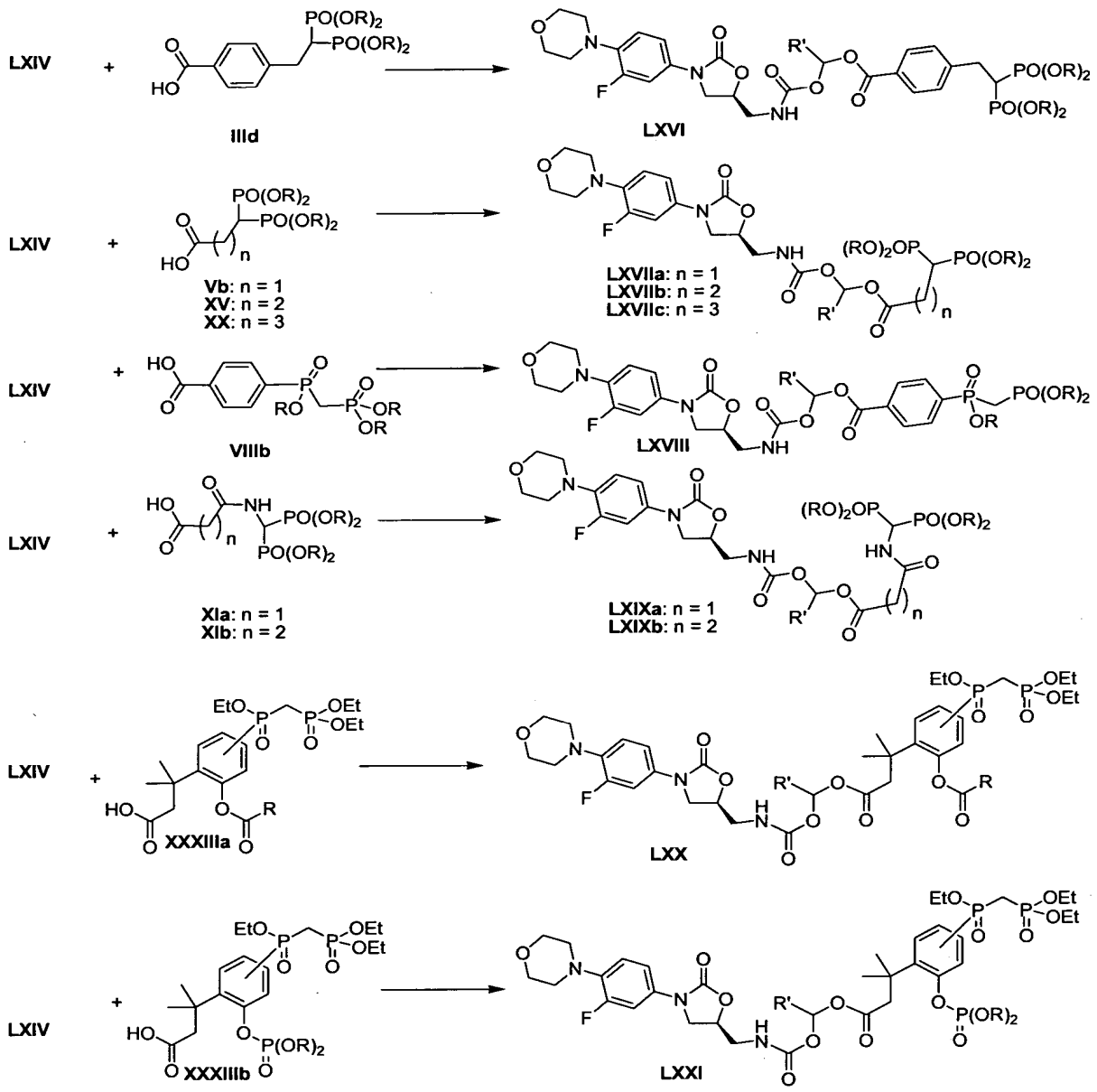
Addition of amine **XLVI** to olefin **XII** can give access to adduct **LXa**. Compound **LXb** is available via condensation of amine **XLVI** with diethyl phosphite and triethyl orthoformate.



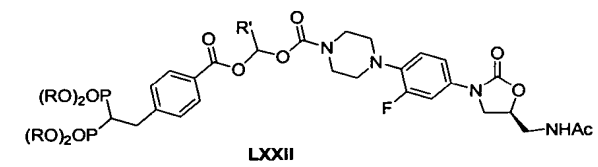
Acylation of amine **XLVI** with bromoacetyl bromide can provide compound **LXI** (J. Am. Chem. Soc. (2004), 126; 1956-1957). Alcohols **XVIIc** and **XVIId** and thiol **XXI** can displace the bromine in the presence of a non nucleophilic base to give access to bisphosphonate conjugates **LXII(a-b)** and **LXIII**.



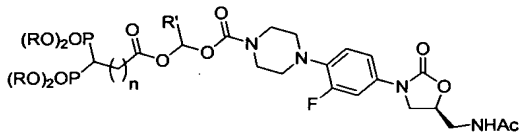
Amine functionalized oxazolidinones such as **XXXIX** and **XLVI** can be acylated with chloroalkyl chloroformates to furnish chloroalkyl carbamates such as **LXIV** and **LXV**.



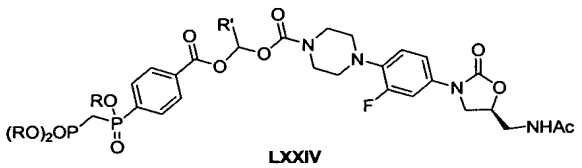
Chloroalkyl carbamate **LXIV** can react with carboxylic acids **IIId, Vb, XV, XX, VIIIb, XI(a-b)** and **XXXIII(a-b)** in the presence of a non nucleophilic base, or with the corresponding carboxylate salts, to furnish bisphosphonates acyloxyalkyl carbamates **LXVI** to **LXXI**.



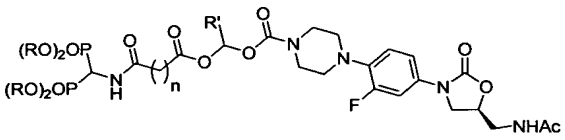
LXXII



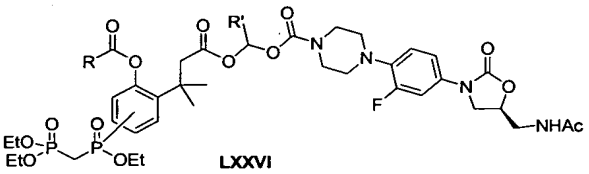
LXXIIIa: n = 1
LXXIIIb: n = 2
LXXIIIc: n = 3



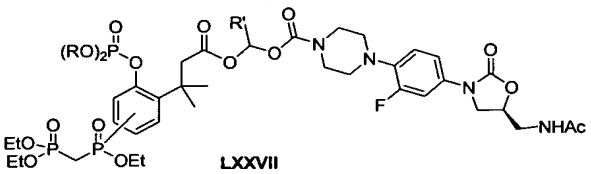
LXXIV



LXXVa: n = 2
LXXVb: n = 3

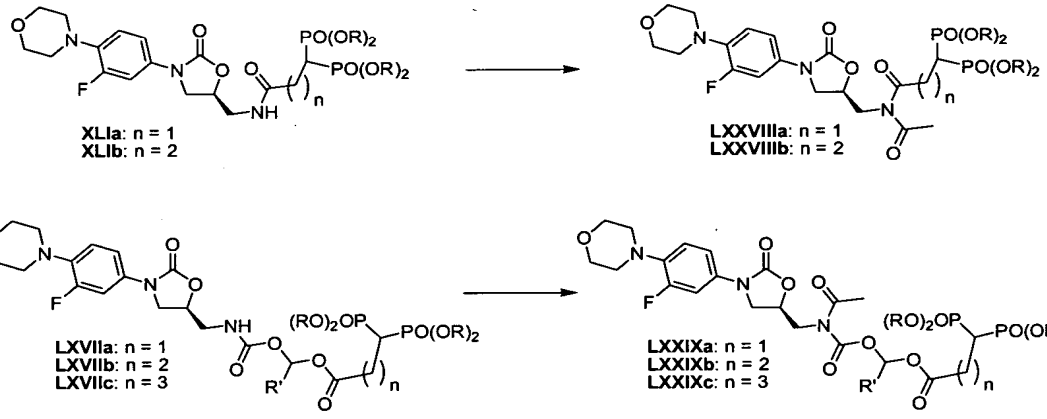


LXXVI



LXXVII

A similar treatment of chloroalkyl carbamate **LXV** with acids **IIId**, **Vb**, **XV**, **XX**, **VIIIb**, **XI(a-b)** and **XXXIII(a-b)** results in the respective acyloxyalkyl carbamates **LXXII** to **LXXVII**.



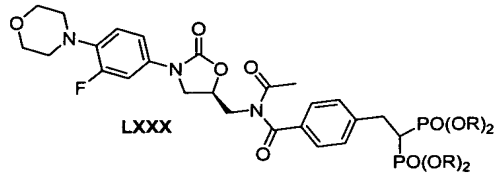
XLIa: n = 1
XLIb: n = 2

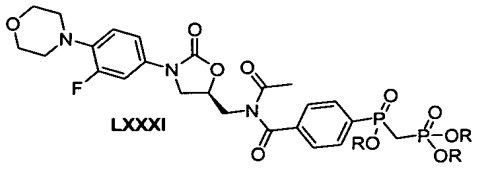
LXXVIIIa: n = 1
LXXVIIIb: n = 2

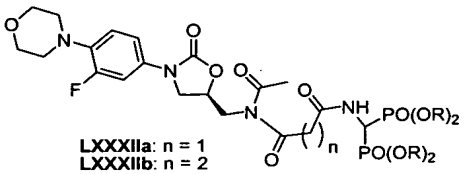
LXVIIa: n = 1
LXVIIb: n = 2
LXVIIc: n = 3

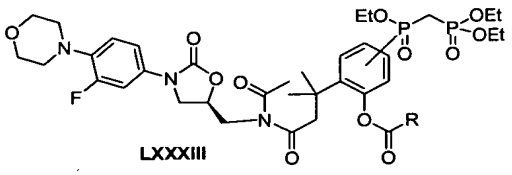
LXXIXa: n = 1
LXXIXb: n = 2
LXXIXc: n = 3

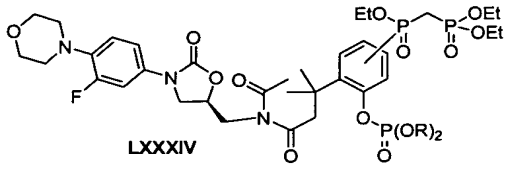
Bisphosphonated amides such as **XLI(a-b)** and carbamates such as **LXVII(a-c)** possessing a secondary nitrogen can be further acetylated to furnish bisphosphonated imides **LXXVIII(a-b)** and **LXXIX(a-c)**.

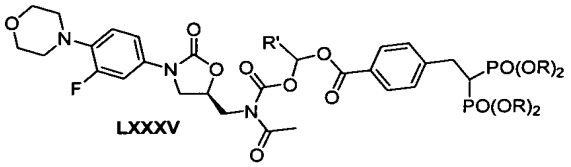


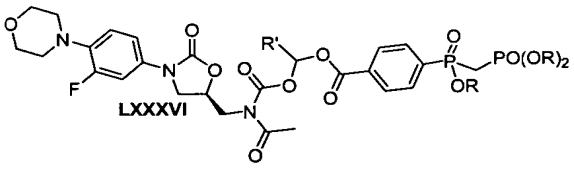


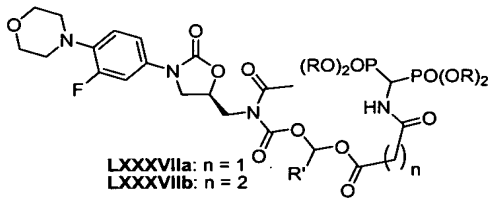


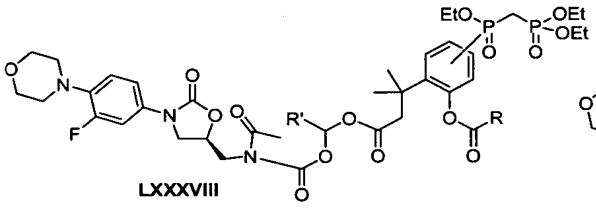


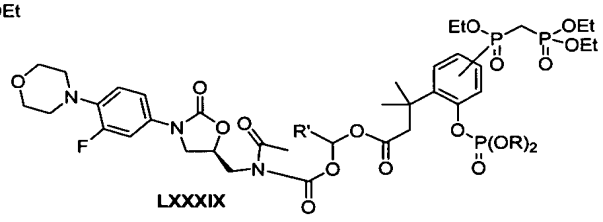




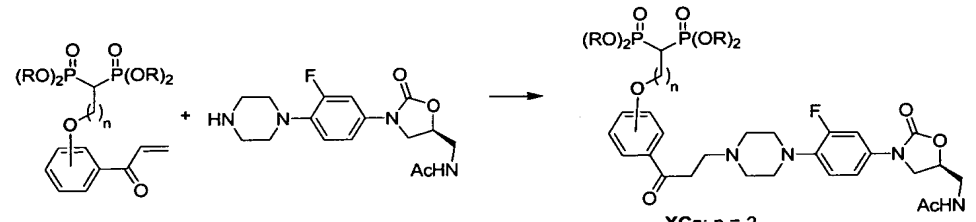








Similarly compounds **XL** and **XLII** to **XLVI** and acyloxycarbamates **LXVI** and **LXVIII** to **LXXI** can be converted to bisphosphonated Linezolid conjugates **LXXX** to **LXXXIX** by acetylation.

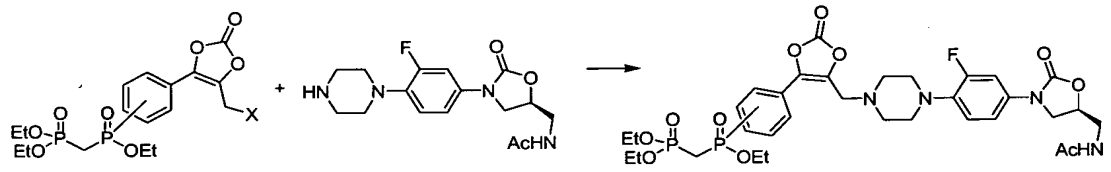


XXIIIa: n = 2
XXIIIb: n = 3
XXIIIc: n = 4

XLVI

XCa: n = 2
XCb: n = 3
XCc: n = 4

Antibacterial oxazolidinones possessing a secondary amine functionality such as **XLVI** can be treated with bisphosphonated enones **XXIII(a-c)** under mildly basic conditions to furnish bisphosphonated oxazolidinone β-aminoketones **XC(a-b)**.



XXVII X = halogen

XLVI

XCI

Treatment of Antibacterial oxazolidinones possessing a secondary amine functionality such as **XLVI** with the bisphosphonated halomethyldioxolone **XXVII** in the presence of a non nucleophilic base furnishes the bisphosphonated dioxolonylmethyl oxazolidinone **XCI**.

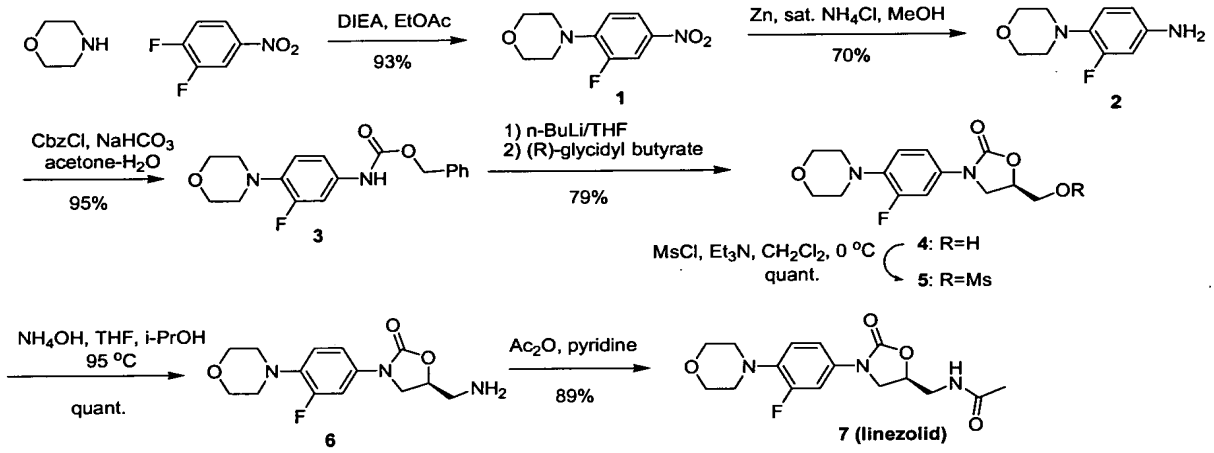
For all bisphosphonated oxazolidinone conjugates, deprotection of the phosphonate esters to provide the corresponding phosphonic acids is undertaken according to the nature of R. If R = Me, Et or *i*-Pr, the ester is treated with TMSBr in a solvent such as CH_2Cl_2 , with or without an amine or a heteroaromatic nitrogen containing base, and the resulting silylated intermediate is hydrolysed with water. When R = Allyl, the esters are hydrolyzed by treatment with a strong nucleophile in the presence of Pd(II) catalysts. When R = Bn, the esters are cleaved by hydrogenolysis using a catalyst such as Pd on carbon in a solvent such as ethanol.

The other protecting groups used can be put on and removed using the coventional methods described in the literature, for instance as reviewed in "*Protective Groups in Organic Synthesis*", Greene, T.W. and Wuts, P.M.G., Wiley-Interscience, New York, 1999.

B) Detailed Experimental Procedures

B-1) Synthesis of linezolid and eperezolid

Scheme 1. Synthesis of linezolid



Linezolid was prepared using a modified protocol derived from *J. Med. Chem.* **1996**, *39*, 673-679.

4-(2-Fluoro-4-nitrophenyl)morpholine (1). Compound **1** was obtained in 93% yield (yellow solid) using the protocol described in *J. Med. Chem.* **1996**, *39*, 673-679. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27-3.29 (m, 4H), 3.86-3.89 (m, 4H), 6.92 (t, *J*=8.6, 1H), 7.92 (dd, *J*=13.1, 2.7, 1H), 8.00 (ddd, *J*=9.2, 2.7, 1.2, 1H).

4-(2-Fluoro-4-aminophenyl)morpholine (2). To a solution of **1** (19.0 g, 84 mmol) in MeOH (375 mL) and saturated NH_4Cl solution (125 mL) cooled in a cold water bath was added Zn (27.0 g, 420 mmol) portionwise. The resulting slurry was stirred for 18 h after which the solids were removed by filtation and washed with 3 × 100 mL MeOH. The combined methanolic solutions were concentrated under reduced pressure to remove just MeOH, resulting in an aqueous solution. On the other hand, the filtered solids were suspended in EtOAc (300 mL), filtered and washed with 3 × 100 mL EtOAc. The organic solutions were combined. The aqueous NH_4Cl solution and organic solution were combined, H_2O was added (100 mL) and the layers were separated. The organic layer was washed with 2 × 200 mL H_2O and saturated NaCl solution (100 mL), dried over Na_2SO_4, filtered and concentrated to yield **2** as an ochre solid (11.5 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96-2.98 (m, 4H), 3.58 (bs, 2H), 3.84-3.86 (m, 4H), 6.39-6.45 (m, 2H), 6.78-6.82 (m, 1H).

Benzyl 3-fluoro-4-morpholinophenylcarbamate (3). Compound **3** was obtained as a beige solid in 95% yield from **2** using the protocol described in *J. Med. Chem.* **1996**, *39*, 673-679.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02-3.05 (m, 4H), 3.86-3.88 (m, 4H), 5.19 (s, 2H), 6.59 (bs, 1H), 6.87-6.91 (m, 1H), 6.96-6.98 (m, 1H), 7.28-7.41 (m, 5H).

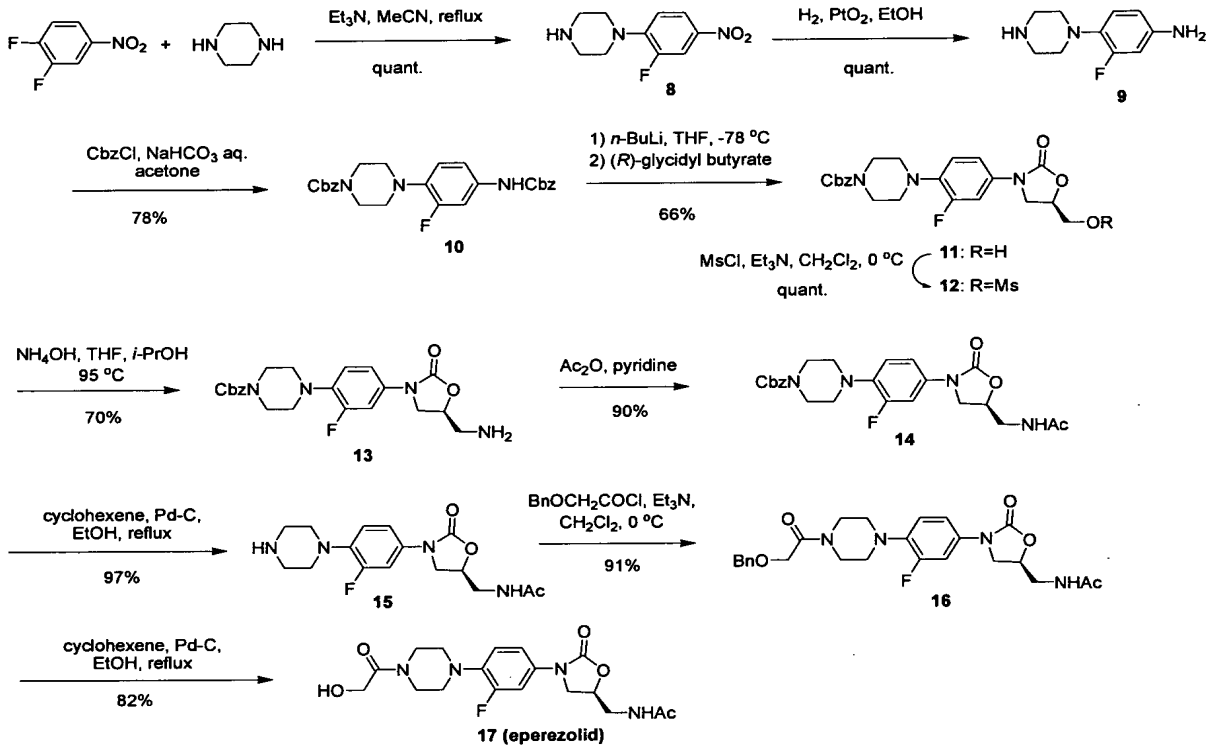
(*R*)-3-(3-Fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one (4). Compound **4** was obtained as a mauve solid in 79% yield from **3** using the protocol described in *J. Med. Chem.* **1996**, *39*, 673-679. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (dd, *J*=7.2, 6.0, 1H), 3.04-3.06 (m, 4H), 3.73-3.79 (m, 1H), 3.86-3.88 (m, 4H), 3.92-4.03 (m, 3H), 4.72-4.77 (m, 1H), 6.93 (t, *J*=9.2, 1H), 7.13 (ddd, *J*=8.8, 2.7, 1.2, 1H), 7.45 (dd, *J*=14.4, 2.6, 1H).

(*R*)-3-(3-Fluoro-4-morpholinophenyl)-5-(methanesulfonyloxymethyl)oxazolidin-2-one (5). Compound **5** was obtained as a mauve solid in quantitative yield from **4** using the protocol described in *J. Med. Chem.* **1996**, *39*, 673-679. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05-3.07 (m, 4H), 3.10 (s, 3H), 3.86-3.88 (m, 4H), 3.92 (dd, *J*=9.1, 6.1, 1H), 4.12 (t, *J*=9.1, 1H), 4.42 (dd, *J*=11.7, 4.2, 1H), 4.50 (dd, *J*=11.7, 3.8, 1H), 4.88-4.94 (m, 1H), 6.94 (t, *J*=9.1H, 1H), 7.11 (ddd, *J*=8.8, 2.7, 1.7, 1H), 7.44 (dd, *J*=14.2, 2.6, 1H).

(*S*)-5-(Aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (6). Methanesulfonate **5** (1.0 g, 2.67 mmol) was suspended in 24 mL 1:1:1 conc. NH_4OH:THF:*i*-PrOH in a pressure tube. The reaction mixture was heated at 95 °C for 18 h, after which the solution was cooled to room temperature, added to 100 mL H_2O and extracted with EtOAc (1 × 100 mL, 2 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to yield **6** as a mauve solid (0.8 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (bs, 2H), 2.96 (dd, *J*=13.7, 5.7, 1H), 3.02-3.05 (m, 4H), 3.09 (dd, *J*=13.7, 4.1, 1H), 3.80 (dd, *J*=8.6, 6.7, 1H), 3.84-3.87 (m, 4H), 3.99 (t, *J*=8.6, 1H), 4.62-4.68 (m, 1H), 6.91 (t, *J*=9.0, 1H), 7.11-7.13 (m, 1H), 7.45 (dd, *J*=14.4, 2.6, 1H).

***N*-[((*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-oxazolidin-5-yl)methyl]acetamide (7, linezolid).** To a solution of amine **6** (800 mg, 2.71 mmol) in pyridine (7 mL) cooled to 0 °C was added Ac_2O (768 μL, 8.13 mmol). The mixture was stirred at 0 °C for 30 min, warmed to room temperature and stirred for an additional 16 h, after which it was concentrated under reduced pressure and purified by flash chromatography using a gradient of 1-5% MeOH / $CHCl_3$ as eluent to provide linezolid (**7**) as an off-white solid (814 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.04-3.06 (m, 4H), 3.57-3.64 (m, 1H), 3.69 (dd, *J*=6.1, 3.2, 1H), 3.71-3.74 (m, 1H), 3.85-3.88 (m, 4H), 4.02 (t, *J*=9.0, 1H), 4.74-4.80 (m, 1H), 6.09 (t, *J*=6.2, 1H), 6.92 (t, *J*=9.1, 1H), 7.08 (ddd, *J*=8.8, 2.6, 1.1, 1H), 7.44 (dd, *J*=14.3, 2.6, 1H). LCMS: 100% (254 nm), 98.9% (220 nm), 96.1% (320 nm). MS : 338 $(MH)^+$.

Scheme 2. Synthesis of eperezolid



1-(2-Fluoro-4-nitrophenyl)piperazine (8). To 3,4-difluoronitrobenzene (20.5 g, 129 mmol) in acetonitrile (290 mL) was added triethylamine (36 mL) and piperazine (32 g, 387 mmol). The mixture was stirred at reflux for 18 h, after which it was cooled to room temperature and partitioned between H_2O (500 mL) and EtOAc (400 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 300 mL). The organic layers were combined and washed with saturated NaCl solution (400 mL). The saturated NaCl layer was extracted again with EtOAc (2 × 200 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to yield **8** as a yellow solid (29 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 1H), 3.04-3.06 (m, 4H), 3.25-3.28 (m, 4H), 6.91 (t, *J*=8.7, 1H), 7.90 (dd, *J*=13.2, 2.5, 1H), 7.97-8.00 (m, 1H).

3-Fluoro-4-(piperazin-1-yl)benzenamine (9). Compound **8** (10.0 g, 44.4 mmol) was dissolved in anhydrous EtOH (222 mL) and placed in a Parr pressure flask. PtO_2 catalyst (31 mg) was added and the mixture was agitated under 50-60 psi of H_2 on a Parr apparatus for 30 min, after which the reaction mixture was vented, more catalyst was added (78 mg) and the reaction mixture was submitted to 50-60 psi of H_2 for another 30 min. The reaction mixture was filtered on Celite, the solid was washed with MeOH, and the combined filtrates were

concentrated to give **9** as a yellow solid (8.7 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (bs, 1H), 2.92-2.94 (m, 4H), 3.02-3.04 (m, 4H), 5.53 (bs, 2H), 6.38-6.45 (m, 2H), 6.80 (t, *J*=8.5, 1H).

Benzyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-3-fluorophenylcarbamate (10). Compound **10** was obtained in 78% yield (light yellow solid) using the protocol described in *J. Med. Chem.* **1996**, *39*, 673-679. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (bs, 4H), 3.65-3.68 (m, 4H), 5.16 (s, 2H), 5.19 (s, 2H), 6.59 (bs, 1H), 6.85 (t, *J*=9.1, 1H), 6.94-6.97 (m, 1H), 7.27-7.41 (m, 11H).

Benzyl 4-(2-fluoro-4-((*R*)-5-(hydroxymethyl)-2-oxo-oxazolidin-3-yl)phenyl) piperazine-1-carboxylate (11). Compound **11** was obtained in 66% yield (off-white solid) using the protocol described in *J. Med. Chem.* **1996**, *39*, 673-679. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (bs, 4H), 3.66-3.69 (m, 4H), 3.74-3.79 (m, 1H), 3.92-4.03 (m, 3H), 4.71-4.77 (m, 1H), 5.16 (s, 2H), 6.91 (t, *J*=9.1, 1H), 7.11-7.14 (m, 1H), 7.91-7.38 (m, 5H), 7.46 (dd, *J*=14.2, 2.5, 1H).

Benzyl 4-(2-fluoro-4-((*R*)-5-(methanesulfonyloxymethyl)-2-oxo-oxazolidin-3-yl)phenyl) piperazine-1-carboxylate (12). Compound **12** was obtained in quantitative yield (off-white foam) using the protocol described in *J. Med. Chem.* **1996**, *39*, 673-679. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (bs, 4H), 3.10 (s, 3H), 3.67-3.69 (m, 4H), 3.92 (dd, *J*=9.1, 6.1, 1H), 4.12 (t, *J*=9.1, 1H), 4.44 (dd, *J*=11.7, 3.8, 1H), 4.49 (dd, *J*=11.7, 3.8, 1H), 4.88-4.94 (m, 1H), 5.16 (s, 2H), 6.93 (t, *J*=9.1, 1H), 7.08-7.12 (m, 1H), 7.30-7.38 (m, 5H), 7.44 (dd, *J*=14.0, 2.6, 1H).

Benzyl 4-(4-((*S*)-5-(aminomethyl)-2-oxo-oxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (13). Compound **13** was obtained in 70% yield from **12** (4.4 g, 8.67 mmol), following the same procedure as for compound **6**. After work-up, crude **13** was purified by flash chromatography using a gradient of 0-2-5-10% MeOH / $CHCl_3$ as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (bs, 2H), 2.94-3.03 (m, 5H), 3.11 (dd, *J*=13.7, 4.1, 1H), 3.66-3.69 (m, 4H), 3.82 (dd, *J*=8.6, 6.7, 1H), 4.00 (t, *J*=8.7, 1H), 4.63-4.69 (m, 1H), 5.16 (s, 2H), 6.91 (t, *J*=9.1, 1H), 7.12-7.15 (m, 1H), 7.30-7.38 (m, 5H), 7.47 (dd, *J*=14.3, 2.6, 1H).

Benzyl 4-(4-((*S*)-5-(acetylaminomethyl)-2-oxo-oxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (14). Compound **14** was obtained in 90% yield from **13** (5.3 g, 12.4 mmol), following the same procedure as for compound **7**. After work-up, the compound was used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.01 (bs, 4H), 3.57-3.77 (m, 7H), 4.01 (t, *J*=9.0, 1H), 4.73-4.79 (m, 1H), 5.16 (s, 2H), 6.05 (t, *J*=6.2, 1H), 6.91 (t, *J*=9.2, 1H), 7.05-7.08(m, 1H), 7.32-7.38 (m, 5H), 7.44 (dd, *J*=14.2, 2.62, 1H).

***N*-[((*S*)-3-(3-fluoro-4-(piperazin-1-yl)phenyl]-2-oxo-oxazolidin-5-yl)methyl)acetamide (15).** To a solution of **14** (748 mg, 1.59 mmol) in abs. ethanol (40 mL) was added cyclohexene (1 mL) and 10% Pd / C (400 mg). The mixture was refluxed for 2 h, when TLC indicated

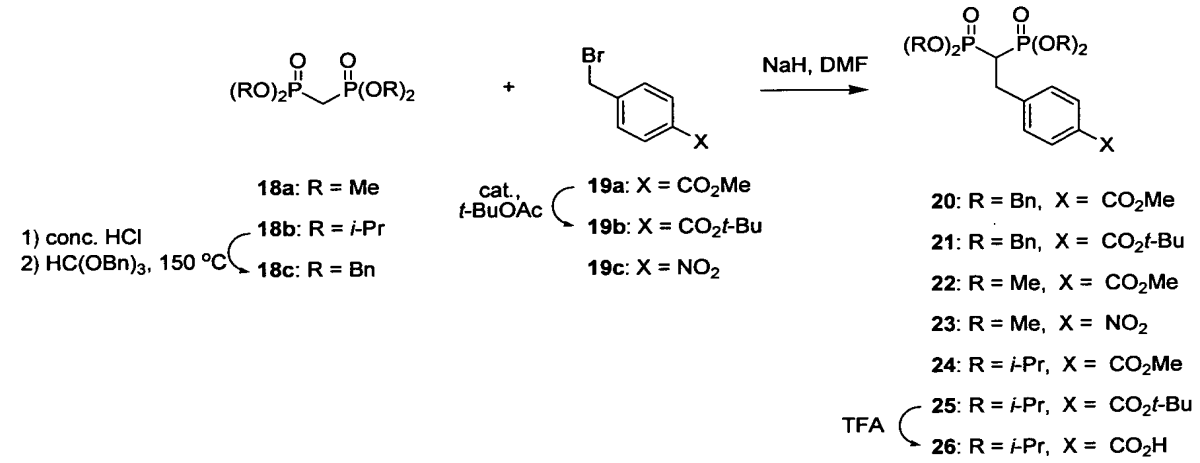
complete reaction. The reaction mixture was filtered through celite and concentrated to give **15** as an off-white solid (520 mg, 97%). The product was essentially pure, but could be purified by chromatography (90:10:1.5 CH_2Cl_2:MeOH:conc. NH_4OH). ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.02 (d, *J*=4.7, 8H), 3.57-3.76 (m, 3H), 4.01 (t, *J*=9.0, 1H), 4.73-4.79 (m, 1H), 6.29 (m, 1H), 6.92 (t, *J*=9.1, 1H), 7.04-7.07(m, 1H), 7.39-7.43 (m, 1H).

***N*-(((*S*)-3-(4-(4-(2-(benzyloxy)acetyl)piperazin-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (16).** To a solution of **15** (537 mg, 1.60 mmol) and triethylamine (0.22 mL, 3.53 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added benzyloxyacetyl chloride (0.30 mL, 1.92 mmol). The mixture was stirred at 0 °C for 1 h, then 15 min at room temperature when TLC indicated complete reaction. The reaction mixture was washed with water (2 × 30 mL), and saturated sodium bicarbonate (2 × 30 mL), and dried over $MgSO_4$. After chromatography (gradient elution 5-10% MeOH / CH_2Cl_2) the product was obtained as a white foam (709 mg, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.98-3.14 (m, 4H), 3.56-3.86 (m, 7H), 4.02 (t, *J*=9.0, 1H), 4.22 (s, 2H), 4.62 (s, 2H), 4.73-4.80 (m, 1H), 6.02 (t, *J*=5.9,1H), 6.96-7.10 (m, 2H), 7.28-7.40 (m, 5H), 7.45-7.53 (m, 1H).

***N*-(((*S*)-3-(3-fluoro-4-(4-(2-hydroxyacetyl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (17, eperezolid).** To a solution of **16** (709 mg, 1.46 mmol) in abs. ethanol (40 mL) was added cyclohexene (1 mL) and 10% Pd / C (250 mg). The mixture was refluxed for 15 h, when TLC indicated complete reaction. The reaction mixture was filtered through Celite™ and concentrated to give **17** (470 mg, 82% yield). The product was essentially pure, but could be purified by chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.06-3.10 (m, 4H), 3.45-3.50 (m, 2H), 3.58-3.77 (m, 3H), 3.85-3.87 (m, 2H), 4.02 (t, *J*=9.0, 1H), 4.21 (s, 2H), 4.74-4.80 (m, 1H), 6.09 (t, *J*=6.0, 1H), 6.97 (t, *J*=9.1, 1H), 7.07-7.10 (m, 1H), 7.46-7.50 (m, 1H). LCMS : 96.1% (254 nm), 95.1% (220 nm), 94.5% (320 nm). MS : 395 $(MH)^+$.

B-2) Synthesis of bisphosphonate scaffolds

Scheme 3. Synthesis of benzyl-substituted bisphosphonate building blocks



Compounds **20-25** were synthesized in a similar fashion to the compounds in *Bioorg. Med. Chem.* **1999**, *7*, 901-919.

Tetrabenzyl methylenediphosphonate (18c). Compound **18c** was synthesized from ester **18b** using the protocol described in *Bioorg. Med. Chem.* **1999**, *7*, 901-919 and was obtained in 75% yield (over 2 steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, *J*=21.1, 2H), 4.98-5.08 (m, 8H), 7.28-7.33 (m, 20H).

***t*-Butyl (4-bromomethyl)benzoate (19b).** Cluster catalyst, NaO*t*-Bu•3NaOC_6H_4-4-*t*-Bu, was prepared by adding NaO*t*-Bu (1.78 g, 18.5 mmol) portionwise to a stirred solution of 4-*t*-butyl phenol (2.09 g, 13.9 mmol) in dry THF (50 mL). The solution was stirred for 30 min at room temperature, resulting in an almost clear solution of the catalyst. The catalyst solution (24 mL, 2.19 mmol) was added to a solution of methyl ester **19a** (10.0 g, 43.7 mmol) in *t*-BuOAc (29 mL, 218 mmol) and the mixture was placed on a rotavapor under a vacuum of 130 Torr and heated at 40 °C for 1 h, after which the mixture was concentrated to dryness. Crude **19b** was purified by flash chromatography, using 25% CH_2Cl_2 / hexane as eluent. Evaporation of the combined fractions yielded **19b** as a colorless oil (8.9 g, 75%), containing 7% of 4-*t*-butyl phenol. ^{1}H NMR of major product (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 4.50 (s, 2H), 7.44 (d, *J*=8.5, 2H), 7.96 (d, *J*=8.4, 2H).

Tetrabenzyl 2-(4-carbomethoxyphenyl)ethane-1,1-diphosphonate (20). Sodium hydride (60% suspension in mineral oil, 225 mg, 5.63 mmol) was added portionwise to a solution of tetrabenzyl methylenediphosphonate (**18c**, 3.00 g, 5.59 mmol) in DMF (10 mL) at room temperature. The mixture was stirred at room temperature for 80 min and a solution of methyl (4-bromomethyl)benzoate (**19a**, 1.41 g, 6.15 mmol) in THF (2 mL) was then added. The mixture

was stirred at room temperature for 40 min, and then quenched with saturated NH_4Cl (15 mL). The reaction mixture was added to water (70 mL) and EtOAc (50 mL). After separation, the aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organics washed with water (3 × 50 mL) and with brine (2 × 50 mL). After drying ($MgSO_4$), filtration and evaporation the residue was purified by flash chromatography (Et_2O:hexanes 2:1, then Et_2O). The pure product was obtained in 54% yield (2.05 g, clear colorless oil). ^1H NMR (400 MHz, $CDCl_3$) δ 2.70 (tt, *J*=23.9, *J*=6.5, 1H), 3.26 (td, *J*=16.6, *J*=6.5, 2H), 3.87 (s, 3H), 4.89-4.99 (m, 8H), 7.08 (dd, *J*=8.3, 2H), 7.18-7.28 (m, 20H), 7.76 (d, *J*=8.3, 2H).

Tetrabenzyl 2-(4-carbo-*t*-butoxyphenyl)ethane-1,1-diphosphonate (21). As for **20** using tetrabenzyl methylenediphosphonate (**18c**) and *t*-butyl 4-(bromomethyl)benzoate (**19b**). Crude product chromatographed in EtOAc / hexanes mixtures, gradient elution. The product was obtained in 51% yield as a clear colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 2.73 (tt, *J*=30.4, *J*=6.6, 1H), 3.28 (td, *J*=16.6, *J*=6.5, 2H), 4.92-4.99 (m, 8H), 7.08 (d, *J*=8.6, 2H), 7.20-7.31 (m, 20H), 7.74 (d, *J*=8.6, 2H).

Tetramethyl 2-(4-carbomethoxyphenyl)ethane-1,1-diphosphonate (22). As for **20**, using tetramethyl methylenediphosphonate (**18a**) and methyl (4-bromomethyl)benzoate (**19a**). The reaction was quenched with saturated NH_4Cl (5 mL), and added to brine (100 mL) and EtOAc (50 mL). After separation the aqueous layer was extracted with EtOAc (2 × 50 mL), dried ($MgSO_4$), evaporated and chromatographed in EtOAc / MeOH mixtures, gradient elution. The product was obtained in 46% yield as a clear colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.68 (tt, *J*=23.8, *J*=6.5, 1H), 3.27 (td, *J*=16.4, *J*=6.5, 2H), 3.70-3.74 (m, 12H), 3.90 (s, 3H), 7.33 (d, *J*=8.1, 2H), 7.96 (d, *J*=8.1, 2H).

Tetramethyl 2-(4-nitrophenyl)ethane-1,1-diphosphonate (23). As for **20**, using tetramethyl methylenediphosphonate (**18a**) and 1-(bromomethyl)-4-nitrobenzene (**19c**). The reaction was quenched with saturated NH_4Cl (5 mL), and added to brine (100 mL) and EtOAc (50 mL). After separation the aqueous layer was extracted with EtOAc (2 × 50 mL), dried ($MgSO_4$), evaporated and chromatographed in EtOAc / MeOH mixtures, gradient elution. The product was obtained in 43% yield as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 2.66 (tt, *J*=23.9, *J*=6.6, 1H), 3.33 (td, *J*=16.2, *J*=6.3, 2H), 3.74-3.78 (m, 12H), 7.44 (d, *J*=8.7, 2H), 8.16 (d, *J*=8.7, 2H).

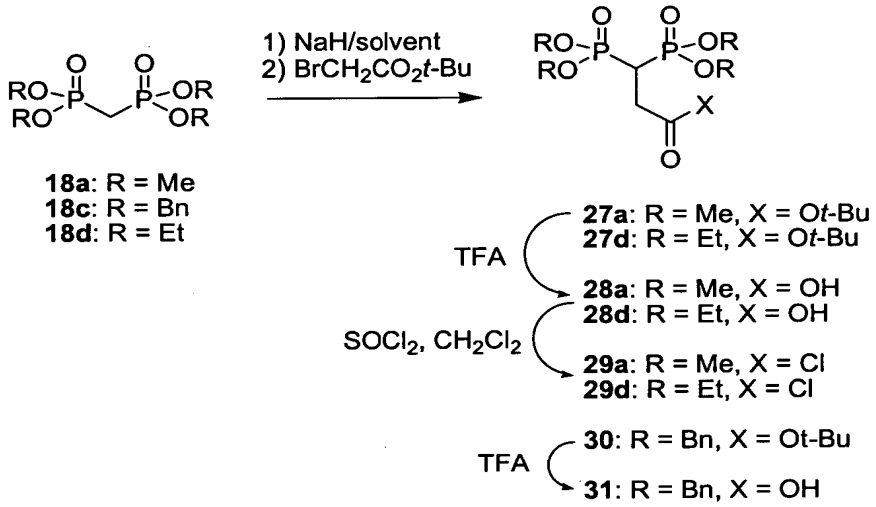
Tetraisopropyl 2-(4-carbomethoxyphenyl)ethane-1,1-diphosphonate (24). As for **20**, using 1.3 equivalents NaH and 1.5 equivalents methyl 4-bromomethylbenzoate (**19a**) to one equivalent of tetraisopropyl methylenediphosphonate (**18b**). Chromatography in EtOAc / MeOH mixtures, gradient elution. The product was obtained in 63% yield as a clear colorless oil. ^1H

NMR (400 MHz, $CDCl_3$) δ 1.22-1.31 (m, 24H), 2.51 (tt, *J*=24.1, *J*=6.3, 1H), 3.25 (td, *J*=16.5, *J*=6.3, 2H), 3.89 (s, 3H), 4.74 (m, 4H), 7.34 (d, *J*=8.4, 2H), 7.93 (d, *J*=8.4, 2H).

Tetraisopropyl 2-(4-carbo-*t*-butoxyphenyl)ethane-1,1-diphosphonate (25). As for **20**, using 1.5 equivalents NaH and 1.5 equivalents *t*-butyl 4-(bromomethyl)benzoate (**19b** to one equivalent of tetraisopropyl methylenediphosphonate (**18b**). The crude product was chromatographed using a gradient of 0-2% MeOH / EtOAc. The product was obtained in 61% yield as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (m, 24H), 1.56 (s, 9H), 2.49 (tt, *J*=24.2, *J*=6.6, 1H), 3.21 (td, *J*=16.6, *J*=10.4, 2H), 4.76 (m, 4H), 7.30 (d, *J*=8.2, 2H), 7.87 (d, *J*=8.2, 2H).

Tetraisopropyl 2-(4-carboxyphenyl)ethane-1,1-diphosphonate (26). Ester **25** (7.10 g, 13.3 mmol) was stirred in TFA (33 mL) for 5 min and concentrated under reduced pressure. Crude product was purified by flash chromatography using 5% MeOH / EtOAc as eluent. Evaporation of the combined fractions yielded **26** as a colorless gum (6.0 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.33 (m, 24H), 2.71 (tt, *J*=24.5, 6.5, 1H), 3.29 (td, *J*=16.8, 6.5, 2H), 4.78 (heptuplet, *J*=6.3, 4H), 7.37 (d, *J*=8.3, 2H), 8.03 (d, *J*=8.3, 2H). LCMS : 100% (254 nm), 100% (220 nm). MS : 477.2 $(M-H)^-$.

Scheme 4. Synthesis of carboxymethyl substituted bisphosphonate building blocks



The compounds above were synthesized in a similar fashion to the compounds in *Bioorg. Med. Chem.* **1999**, *7*, 901-19.

Tetramethyl 2-*t*-butoxycarbonylethylene-1,1-bisphosphonate (27a). To a solution of tetramethyl methylenebisphosphonate (**18a**, 5.1 g, 22.0 mmol) in dry DMF (44 mL) was added NaH (60% suspension in mineral oil, 916 mg, 22.0 mmol) portionwise. The resulting slurry was

stirred for 1 h at room temperature, after which a solution of *t*-butyl bromoacetate (6.4 g, 33.0 mmol) in DMF (15 mL) was added dropwise. The reaction mixture was stirred for 30 min and quenched by adding 50 mL of a saturated solution of NH_4Cl. The reaction mixture was added to 200 mL of saturated NaCl solution and extracted with EtOAc (3 × 200 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **27a** as a yellow oil (6.5 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.74 (td, *J*=16.1, 6.2, 2H), 3.11 (tt, *J*=24.0, 6.2, 1H), 3.79 (dd, *J*=11.1, 0.7, 12H).

Tetraethyl 2-*t*-butoxycarbonylethylene-1,1-bisphosphonate (27d): To a solution of tetraethyl methylenebisphosphonate (3.00 g, 10.4 mmol) in dry DMF (9 mL) was added NaH (60% suspension in mineral oil, 0.46 g, 11.5 mmol) portionwise. The resulting slurry was stirred for 30 min at room temperature, after which *t*-butyl bromoacetate (1.7 mL, 11.5 mmol) was quickly added neat. The reaction mixture was stirred for 1 h and quenched by adding 2 mL of a saturated solution of NH_4Cl. The reaction mixture was evaporated and purified by flash chromatography on silica gel eluting with 5% methanol/ethyl acetate to give pure **27d** (2.1 g, 50%) as a clear colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (bt, *J*=7.0, 12H), 1.46 (s, 9H), 2H), 2.76 (td, *J*=16.0, 6.1, 2H), 3.07 (tt, *J*=24.0, 6.1, 1H), 4.10-4.25 (m, 8H).

Tetramethyl 2-carboxyethylene-1,1-bisphosphonate (28a). Ester **27a** (6.50 g, 18.8 mmol) was stirred in TFA (47 mL) for 5 min and concentrated under reduced pressure. Crude acid was purified by flash chromatography using 10% MeOH / CH_2Cl_2 as eluent. Evaporation of combined pure fractions yielded acid **28a** as a white solid (4.5 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (td, *J*=16.2, 6.2, 2H), 3.19 (tt, *J*=24.1, 5.8, 1H), 3.83 (dd, *J*=11.2, 2.7, 12H).

Tetraethyl 2-carboxyethylene-1,1-bisphosphonate (28d): Ester **27d** (2.1 g, 5.2 mmol) was stirred in TFA (12 mL) for 2.5 min and concentrated under reduced pressure. Crude acid **28d** was purified by flash chromatography (gradient elution 100% ethyl acetate – 10% methanol/ ethyl acetate). Acid **28d** was obtained as a white solid (1.35 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.39 (m, 12H), 2.86 (td, *J*=16.1, 6.3, 2H), 3.12 (tt, *J*=24.0, 6.3, 1H), 4.13-4.26 (m, 8H).

Tetramethyl 2-chlorocarbonylethylene-1,1-bisphosphonate (29a). To acid **28a** (252 mg, 0.87 mmol) in CH_2Cl_2 (9 mL) was added $SOCl_2$ (317 μL, 4.34 mmol). The mixture was stirred at reflux for 3 h, concentrated to dryness and co-evaporated with benzene to provide **29a** as a colorless oil (267 mg, quant.) which was immediately used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (tt, *J*=23.7, 6.0, 2H), 3.41 (td, *J*=15.0, 6.1, 1H), 3.83 (dd, *J*=11.2, 1.2, 12H).

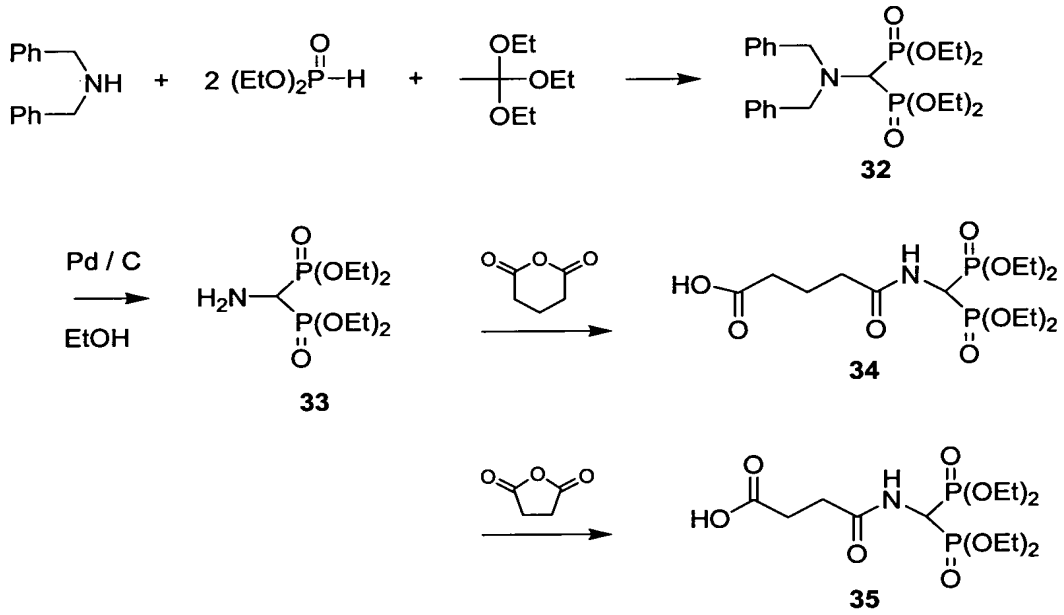
Tetraethyl 2-chlorocarbonylethylene-1,1-bisphosphonate (29d): To acid **28d** (1.02 g, 2.95 mmol) in CH_2Cl_2 (15 mL) was added freshly distilled $SOCl_2$ (0.84 mL, 11.6 mmol). The

mixture was stirred at reflux for 3 h and concentrated to dryness to give crude **29d** as a colourless oil (quantitative) which was immediately used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.40 (m, 12H), 3.05 (tt, *J*=23.5, 6.2, 1H), 3.40 (td, *J*=14.8, 6.2, 2H), 3.12 (tt, *J*=24.0, 6.3, 1H), 4.13-4.27 (m, 8H).

***t*-Butoxycarbonyl tetrabenzyl 2,2-bisphosphonoethane (30).** To a solution of tetrabenzyl methylenebisphosphonate (**18c**, 1.00 g, 1.86 mmol) in dry THF (100 mL) was added NaH (60% suspension in mineral oil, 90 mg, 2.2 mmol) portionwise. The resulting slurry was stirred for 1 h at room temperature, after which a solution of *t*-butyl bromoacetate (544 mg, 2.79 mmol) was added dropwise. The reaction mixture was stirred for 60 min and quenched by adding 50 mL of a saturated solution of NH_4Cl. The reaction mixture was added to 200 mL of saturated NaCl solution and extracted with EtOAc (3 × 200 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using 3 / 2 EtOAc / hexanes as eluent. The product was obtained in 46% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.82 (td, *J*=16.4, 6.1, 2H), 3.30 (tt, *J*=24.0, 6.1, 1H), 5.02 (m, 8H), 7.28 (m, 20H).

Oxycarbonyl tetrabenzyl 2,2-bisphosphonoethane (31). Ester **30** (556 mg, 0.85 mmol) was stirred in TFA (3 mL) for 2 min and concentrated under reduced pressure. Crude acid was purified by flash chromatography using 5% MeOH / CH_2Cl_2 as eluent. Evaporation of combined pure fractions yielded **31** as a colorless oil (501 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (td, *J*=16.4, 5.6, 2H), 3.21 (tt, *J*=26.6, 5.6, 1H), 4.88 (m, 8H), 7.15 (m, 20H).

Scheme 5. Synthesis of 4-[(tetraethyl bisphosphonomethyl)carbamoyl]butanoic acid (34) and 3-[(tetraethyl bisphosphonomethyl)carbamoyl]propanoic acid (35).



***N,N*-Dibenzylamino tetraethyl bisphosphonomethane (32).** Compound **32** was prepared according to a modified protocol derived from *Synth. Comm.* **1996**, *26*, 2037-2043. Triethyl orthoformate (8.89 g, 60 mmol), diethyl phosphite (16.57 g, 120 mmol) and dibenzyl amine (11.80 g, 60 mmol) were combined in a 100 mL round bottom flask fitted with a distillation head. The reaction was heated to a temperature of 180–195 °C for 1 h under Ar. When EtOH evolution was complete, the reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (300 mL), washed with aqueous NaOH (2M, 3 × 60 mL) and brine (2 × 75 mL), then dried over $MgSO_4$. After evaporation, a crude yield of 25.2 g (87%) was obtained. A 4.95 g portion of the crude oil was purified by chromatography (ethyl acetate:hexane:methanol 14:4:1) to yield pure **35** (2.36 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (dt, *J*=2.0, 7.0, 12H), 3.55 (t, *J*=25.0, 1H), 3.95-4.25 (m, 12H), 7.20-7.45 (m, 10H).

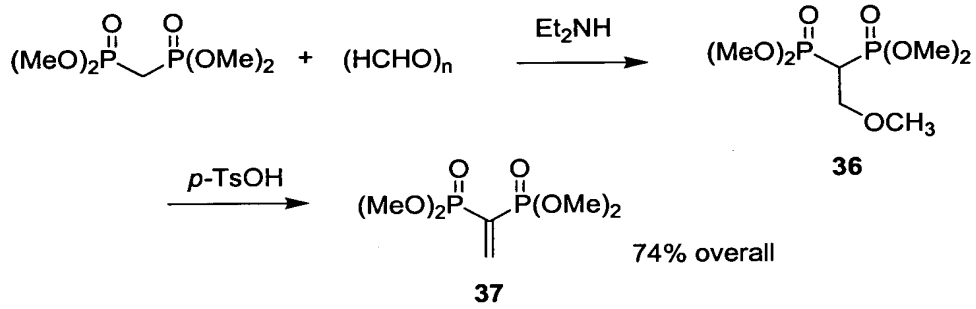
Amino tetraethyl bisphosphonomethane (33). Compound **32** (2.00 g, 4.14 mmol) was dissolved in EtOH (40 mL). To this solution was added palladium on carbon (10%, 1.5 g) and cyclohexene (2.5 mL, 24.7 mmol). The reaction mixture was refluxed under argon for 15 hours, filtered through celite and evaporated to give **33** as a slightly impure pale yellow oil (1.50 g, 119%), which was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J*=7.0, 12H), 3.58 (t, *J*=20.3, 1H), 3.65-3.90 (br s, 2H), 4.20-4.28 (m, 8H).

4-[(tetraethyl bisphosphonomethyl)carbamoyl]butanoic acid (34). Compound **34** was prepared as described in *J. Drug Targeting*, **1997**, *5*, 129-138. It was obtained as an

orange oil, in 85% crude yield from **33**. The crude product could be purified by chromatography (10% AcOH / EtOAc) to give a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J*=7.0, 6H), 1.34 (t, *J*=7.0, 6H), 1.92-2.02 (m, 2H), 2.38-2.44 (m, 2H), 2.54 (t, *J*=7.3, 1H), 4.04-4.28 (m, 8H), 5.16 (td, *J*=22.1, *J*=10.0, 1H), 8.45 (d, *J*=10.2, 1H).

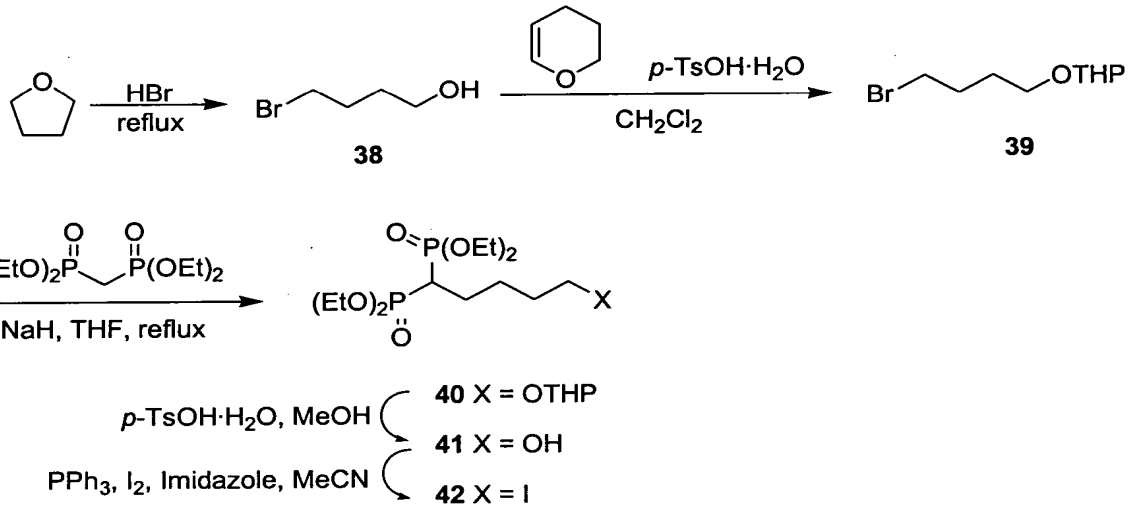
3-[(tetraethyl bisphosphonomethyl)carbamoyl]propanoic acid (35). Compound **35** was prepared as described in *J. Drug Targeting*, **1997**, *5*, 129-138. It was obtained as an oil which slowly solidified, in 57% crude yield from **33**. The crude product could be purified by chromatography (10% AcOH / EtOAc) to give a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J*=7.0, 6H), 1.33 (t, *J*=7.1, 6H), 2.61-2.73 (m, 4H), 4.05-4.28 (m, 8H), 5.07 (td, *J*=21.6, *J*=9.8, 1H), 7.90 (d, *J*=9.4, 1H).

Scheme 6.Synthesis of tetramethyl ethenylidenebisphosphonate (37).



Tetramethyl ethenylidenebisphosphonate (36). Compound **37** was prepared as described in *J. Org. Chem.* **1986**, *51*, 3488-3490. **37** was obtained as a clear liquid in 74% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78-3.81 (m, 12H), 6.94-7.12 (m, 2H).

Scheme 7. Synthesis of tetraethyl 5-iodopentylene-1,1-bisphosphonate (42).



4-Bromo-1-butanol (38): To 67.5 mL (832.2 mmol) of refluxing tetrahydrofuran was added 31 mL (274 mmol) of 48 % hydrobromic acid dropwise and the yellow solution was allowed to reflux for another 2h. After cooled to room temperature, the reaction was carefully neutralized with saturated sodium bicarbonate aqueous solution. The resultant mixture was extracted with diethyl ether (3x) and dried over anhydrous sodium sulfate. Removal of the solvent afforded the product **38** as a yellow oil (10.7 g, 26 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69-1.76 (m, 2H), 2.01-1.94 (m, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.70 (t, *J* = 6.4 Hz, 2H).

2-(4-Bromobutoxy)-tetrahydro-2*H*-pyran (39): 3,4-Dihydro-2*H*-pyran (8.5 mL, 90.96 mmol) was added dropwise to the dichloromethane (20 mL) solution of **38** (10.7 g, 69.93 mmol) and *p*-toluenesulfonic acid monohydrate (26.5 mg, 0.1372 mmol). The mixture was stirred at room temperature over night. After removing the solvent, the residue was purified by flash chromatography on silica gel with 5:1 hexanes/ethyl acetate as the eluent to yield product **39** as a colorless oil (15.3 g, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48-1.62 (m, 4H), 1.68-1.85 (m, 4H), 1.94-2.02 (m, 2H), 3.40-3.53 (m, 4H), 3.74-3.88 (m, 2H), 4.57-4.59 (m, 1H).

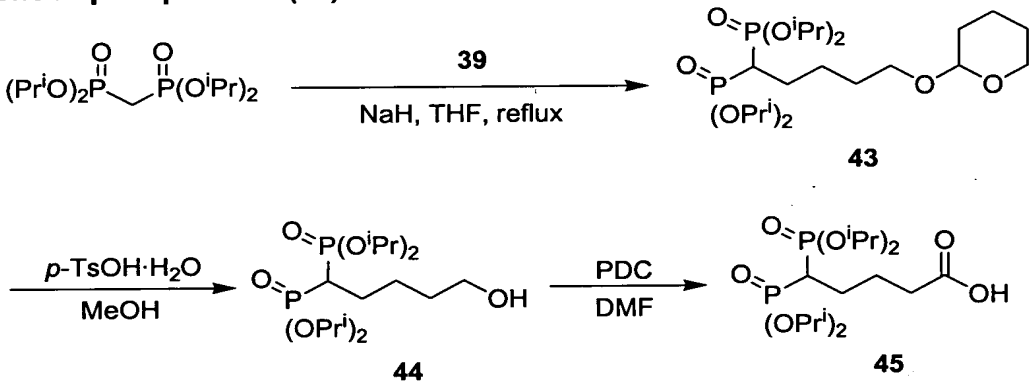
Tetraethyl 5-(2-Tetrahydro-2*H*-pyranyloxy)pentylene-1,1-bisphosphonate (40): To the suspension of sodium hydride (60 %, 840.5 mg, 21.01 mmol) in 40 mL of THF was carefully added tetraethyl methylenebisphosphonate (6.16 g, 20.95 mmol) and the resultant pale yellow clear solution was stirred at room temperature for 45 min. Then the bromide **39** (4.97 g, 20.96 mmol) was introduced plus 5 mL of THF rinse. The reaction was brought to reflux overnight and allowed to cool to room temperature before being quenched with saturated ammonium chloride aqueous solution. Another small amount of water was required to dissolve the solid. The mixture was extracted with ethyl acetate (3x), dried over anhydrous sodium sulfate and concentrated *in*

vacuo. Flash chromatography on silica gel with 20:1 (v/v) dichloromethane/methanol as the eluent afforded 7.3 g of impure product **40** as a slightly yellow oil. The material was used directly in the next step without further purification. Selected ^{1}H NMR signals (400 MHz, $CDCl_3$): δ 2.28 (tt, *J*=6.1, 24.3 Hz, 1H), 3.37-3.51 (m, 2H), 3.71-3.89 (m, 2H), 4.56-4.58 (m, 1H).

Tetraethyl 5-hydroxypentylene-1,1-bisphosphonate (41). The crude compound **40** was dissolved in 20 mL of methanol and 74.6 mg (0.3863 mmol) of *p*-toluenesulfonic acid monohydrate was added. After overnight stirring at room temperature, the mixture was concentrated and subjected to flash chromatography with gradient elution from 15:1 ethyl acetate/methanol to 8:1 then 6:1 to afford **41** as a colorless oil (3.1 g, 41 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24-1.36 (m, 12H), 1.55-1.72 (m, 4H), 1.89-2.03 (m, 2H), 2.16 (bs, 1H), 2.29 (tt, *J*=6.1, 24.3 Hz, 1H), 3.66 (bs, 2H), 4.11-4.22 (m, 8H).

Tetraethyl 5-iodopentylene-1,1-bisphosphonate (42). The alcohol **41** (1.419 g, 3.938 mmol), triphenylphosphine (1.25 g, 4.718 mmol) and imidazole (325.6 mg, 4.735 mmol) were dissolved in 15 mL of dry acetonitrile, and 1.196 g (4.703 mmol) of I_2 was added in several portions. After overnight stirring at room temperature, the solvent was removed in vacuo and the residue was taken up in ethyl acetate and saturated $Na_2S_2O_3$ aqueous solution. The mixture was stirred until the organic layer turned pale yellow and the two phases were separated. The organic phase was dried over anhydrous sodium sulfate and concentrated. Flash chromatography on silica gel with 15:1 ethyl acetate/methanol as the eluent afforded the product **42** as a yellow oil (1.26 g, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, *J*=7.0 Hz, 12H), 1.66-1.72 (m, 2H), 1.81-1.99 (m, 4H), 2.35 (tt, *J*=5.9, 24.1 Hz, 1H), 3.20 (t, *J*=6.9 Hz, 2H), 4.17-4.23 (m, 8H).

Scheme 8. Synthesis of α-(3-hydroxycarbonylpropyl)-tetraisopropyl methylenebisphosphonate (45).



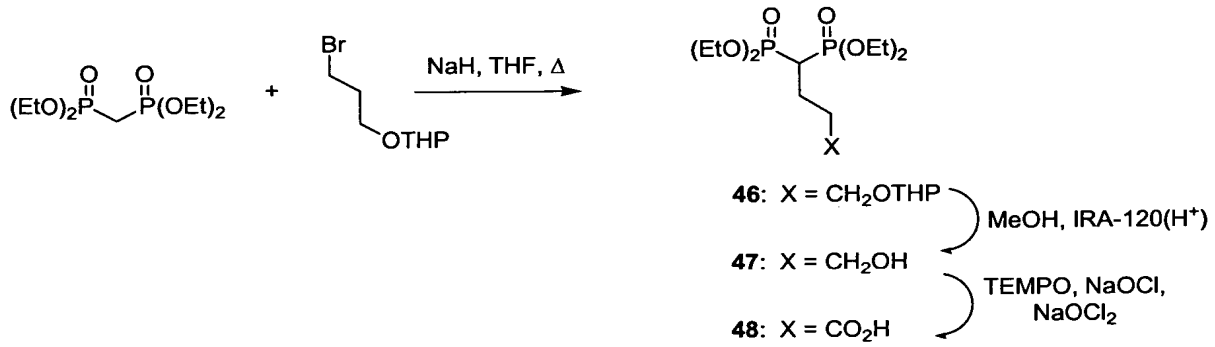
α-(2-Tetrahydro-2H-pyranyloxy)-butyl tetraisopropyl methylenebisphosphonate (43). To a suspension of sodium hydride (60%, 342.5 mg, 8.563 mmol) in 15 mL THF was carefully added tetraisopropyl methylenebisphosphonate (2.80 mL, 8.61 mmol), and the resultant

pale yellow clear solution was stirred at room temperature for 30 min. Then compound **39** (2.0194 g, 8.516 mmol) was introduced plus 5 mL of THF rinse. The reaction was brought to reflux for 8 h and allowed to cool to room temperature before quenching with saturated NH_4Cl. The mixture was extracted with ethyl acetate (3 x) and dried over Na_2SO_4. Flash chromatography with 10:1 EtOAc:MeOH as eluent recovered 760 mg of unreacted starting material **39**. The desired product **43** was not isolable from the other unreacted starting material tetraisopropyl methylenebisphosphonate and the mixture was used directly in the next step. Selected ^1H NMR signals (400 MHz, $CDCl_3$) δ 1.48-2.02 (m, 12H), 2.14 (tt, *J*=24.2, 5.9, 1H), 3.36-3.42 (m, 1H), 3.46-3.52 (m, 1H), 3.71-3.77 (m, 1H), 3.83-3.89 (m, 1H), 4.57-4.58 (m, 1H).

α-(4-Hydroxybutyl)-tetraisopropyl methylenebisphosphonate (44). The mixture from the flash chromatography in the previous step was dissolved in 4 mL of MeOH and 24.5 mg (0.127 mmol) *p*-toluenesulfonic acid monohydrate was added. After stirring overnight at room temperature, the reaction was finished. The mixture was concentrated and subjected to flash chromatography with 12:1 EtOAc:MeOH as eluent to afford **44** as a colorless oil (1.2 g, 50% over two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 1.33-1.36 (m, 24H), 1.54-1.61 (m, 2H), 1.65-1.72 (m, 2H), 1.84-1.98 (m, 2H), 2.15 (tt, *J*=24.1, 6.1, 1H), 2.28 (t, *J*=5.7, 1H), 3.66 (q, *J*=6.1, 2H), 4.72-4.82 (m, 4H).

α-(3-Hydroxycarbonylpropyl)-tetraisopropyl methylenebisphosphonate (45). Compound **44** (365.5 mg, 0.9083 mmol) and pyridinium dichromate (1.22 g, 3.18 mmol) were dissolved in 3 mL *N,N*-dimethyl formamide and stirred at room temperature overnight. After reaction was complete as monitored by TLC, the mixture was diluted with water and extracted with EtOAc (3 x) and dried over Na_2SO_4. Flash chromatography on silica gel with 19:1 EtOAc:acetic acid afforded **45** as a colorless oil (246.8 mg, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.29-1.35 (m, 24H), 1.90-1.99 (m, 4H), 2.18 (tt, *J*=24.4, 5.5, 1H), 2.34 (t, *J*=6.8, 2H), 4.73-4.82 (m, 4H).

Scheme 9. Preparation of tetraethyl 3-carboxypropylene-1,1-bisphosphonate (48):



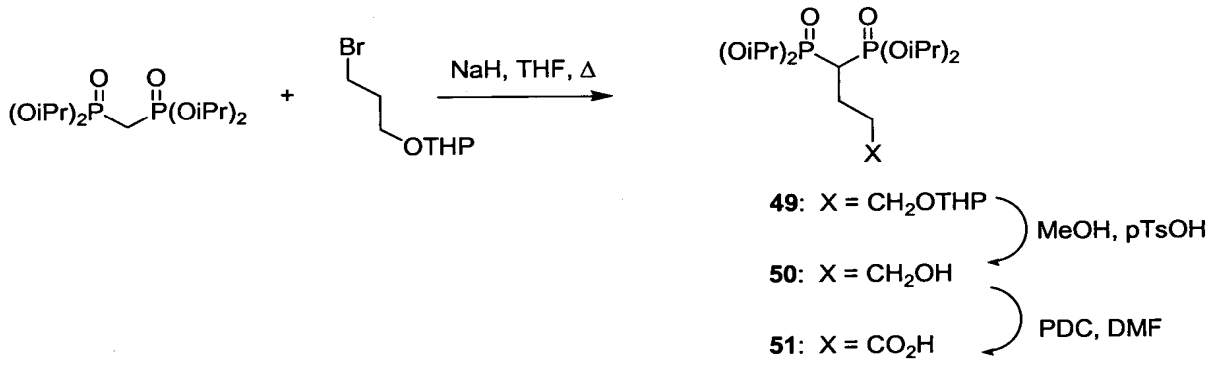
Tetraethyl 4-(2-Tetrahydro-2*H*-pyranyloxy)butylene-1,1-bisphosphonate (46). To a suspension of NaH (60% suspension in mineral oil, 900 mg, 22.0 mmol) in dry THF (20 mL) was added dropwise tetraethyl methylenebisphosphonate (6.46 g, 22.4 mmol). The resulting clear solution was stirred 15 min at room temperature, after which 2-(3-bromopropoxy)tetrahydro-2*H*-pyran (5.05 g, 22.6 mmol) was added dropwise. The reaction mixture was heated to reflux for 6 h, diluted with CH_2Cl_2 (75 mL) and washed with brine (2 x 50 mL), dried ($MgSO_4$) and evaporated. It was used as such in the following step.

Tetraethyl 4-hydroxybutylene-1,1-bisphosphonate (47). To a stirred solution of the crude product **46** (max. 22.4 mmol) in MeOH (40 mL) was added Amberlite IR-120 (0.6 g). The reaction mixture was heated to 50 °C for 4 h, filtered and evaporated. The crude product was purified by flash chromatography on silica gel with gradient elution from 5-10% methanol / ethyl acetate to give pure **47** (2.67 g, 34% from tetraethyl methylenebisphosphonate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*= 7.1 Hz, 12H), 1.81 (quint, *J*= 6.5 Hz, 2H), 1.99-2.13 (m, 2H), 2.37 (tt, *J*= 24.4, 5.6 Hz, 1H), 2.51 (t, *J*=5.9 Hz, 2H), 3.66 (q, *J*= 5.9 Hz, 2H), 4.13-4.22 (m, 8H).

Tetraethyl 3-carboxypropylene-1,1-bisphosphonate (48). To a solution of alcohol **47** (12.7 g, 36.7 mmol) in MeCN (200 mL) and phosphate buffer solution (200 mL, made from mixing equal volumes of 0.67M Na_2HPO_4 solution and 0.67M NaH_2PO_4 solution) at 35 °C was added a catalytic amount of TEMPO (430 mg, 2.75 mmol). The reaction flask, maintained at 35 °C, was fitted with two addition funnels. One was filled with a solution of $NaClO_2$ (8.3 g, 91.7 mmol) in 75 mL H_2O. The other one was filled with a solution of household bleach (5.25%, 25 mL) in 250 mL H_2O. About 1/5 of the $NaClO_2$ solution was added, followed by about 1/5 of the bleach solution to initiate the reaction. The remainder of both solutions was added dropwise, simultaneously, with a rate adjusted so that both additions finished concurrently. The reaction mixture was

stirred at 35 °C for 4 h, then at room temperature for 18 h. The reaction mixture was diluted with 300 mL H_2O and the pH of the solution was adjusted to 8.0 by adding 1M NaOH. The resulting solution was cooled to 0 °C and a cold solution of Na_2SO_3 (6.1% wt, 185 mL) was added slowly. The mixture was stirred at 0 °C during 30 min, after which a portion of Et_2O was added. After stirring vigourously, the mixture was poured into an extraction funnel and the Et_2O layer was separated and discarded. The aqueous layer was acidified to pH 3.4 with conc. HCl and extracted 3 × with $CHCl_3$ / *i*-PrOH mixture (4:1). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to dryness, yielding **48** as a pale yellow oil (12.9 g, 98%), which could be used without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* =7.0 Hz, 12H), 2.18-2.28 (m, 2H), 2.60 (tt, *J*= 23.9, 6.5 Hz, 1H), 2.69 (t, *J*= 7.3 Hz, 2H), 4.14-4.23 (m, 8H)..

Scheme 10. Preparation of tetraisopropyl 3-carboxypropylene-1,1-bisphosphonate (51):



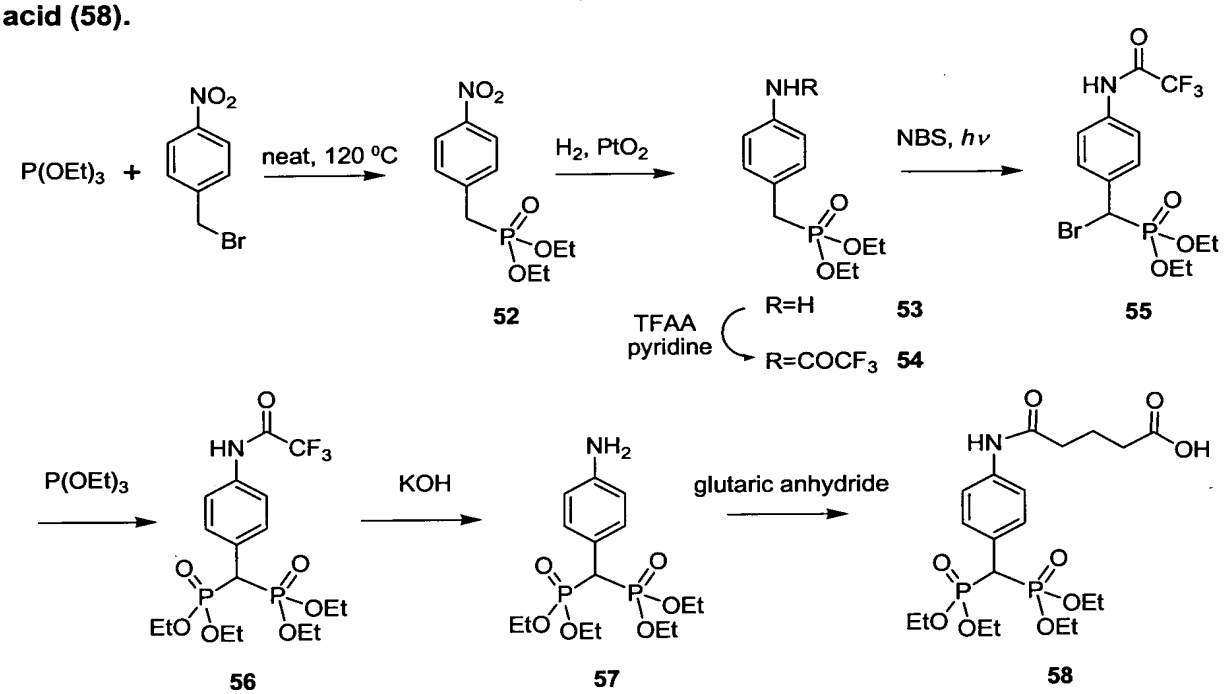
Tetraisopropyl 4-(2-Tetrahydro-2*H*-pyranyloxy)butylene-1,1-bisphosphonate (49). To a suspension of NaH (60% suspension in mineral oil, 1.31 g, 31.4 mmol) in dry THF (32 mL) was added dropwise tetraisopropyl methylenebisphosphonate (10 mL, 31.4 mmol). The resulting clear solution was stirred 15 min at room temperature, after which 2-(3-bromopropoxy)tetrahydro-2*H*-pyran (7.00 g, 31.4 mmol) was added dropwise. The reaction mixture was heated to reflux for 5 h and washed with saturated ammonium chloride solution. The aqueous phase was extracted with CH_2Cl_2 (1x200 mL and 2x100 mL) and the combined organic phase was dried over $MgSO_4$. Flash chromatography on silica gel with the elution of 5 % ethanol in ethyl acetate afforded product **49** (1.5 g, 10 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-1.36 (m, 24H), 1.48-2.06 (m, 10H), 2.20 (tt, *J* = 24.3, 5.7, 1H), 3.39 (dt, *J* = 9.8, 6.1, 1H),

3.46-3.52 (m, 1H), 3.74 (dt, *J* = 9.8, 6.1, 1H), 3.82-3.88 (m, 1H), 4.57-4.60 (m, 1H), 4.74-4.84 (m, 4H).

Tetraisopropyl 4-hydroxybutylene-1,1-bisphosphonate (50). To a stirred solution of compound **49** (1.5 g, 3.083 mmol) in MeOH (10 mL) was added 15.2 mg (0.0787 mmol) of *p*-TsOH monohydrate. After 6 h, reaction was complete as indicated by TLC and the concentrated material was subject to flash chromatography on silica gel with the elution of 20:1 (v/v) dichloromethane/methanol to give pure **50** (862 mg, 70 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (dd, *J* = 6.1, 3.8, 24H), 1.81 (quint, *J* = 6.7, 2H), 1.97-2.11 (m, 2H), 2.21 (tt, *J* = 24.8, 5.3, 1H), 2.81 (t, *J* = 6.1, 1H), 3.67 (q, *J* = 5.7, 2H), 4.77 (sept, *J* = 6.3, 4H).

Tetraisopropyl 3-carboxypropylene-1,1-bisphosphonate (51). To a solution of alcohol **50** (1.19 g, 2.957 mmol) in 15 mL of DMF was added 3.98 g (10.37 mmol) of PDC. The dark solution was stirred at room temperature overnight prior to the dilution with 100 mL of water. The mixture was extracted with ethyl acetate (3x) and dried over sodium sulfate. The product **51** (850 mg, 69 %) was isolated from a flash chromatography on silica gel with the elution of 20:1 (v/v) ethyl acetate/acetic acid as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.37 (m, 24H), 2.12-2.28 (m, 2H), 2.40 (tt, *J* = 24.1, 6.8, 1H), 2.69 (t, *J* = 7.0, 1H), 4.70-4.82 (m, 4H).

Scheme 10. Synthesis of 4-(4-(di(ethoxyphosphono)methyl)phenylcarbamoyl)butanoic acid (58).



Diethyl (4-nitrophenyl)methylphosphonate (52). A neat solution of 4-nitrobenzylbromide (8.4 g, 39 mmol) and triethylphosphite (7.5 mL, 43 mmol) was stirred while heating to 120 °C in a sealed tube for 2 h. The mixture was then cooled and excess triethylphosphite was removed under high vacuum. The crude product was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J*=7.1, 6H), 3.24 (d, *J*=23.1, 2H), 4.01-4.10 (m, 4H), 7.47 (dd, *J*=8.7, 2.4, 2H), 8.18 (d, *J*=8.3, 2H).

Diethyl (4-(2,2,2-trifluoroacetamido)phenyl)methylphosphonate (54). Crude **52** was dissolved in abs. EtOH and hydrogenated over PtO_2 (200 mg) under H_2 (60 psi) for 4 h. The catalyst was filtered off and the solvent removed resulting in the pale-brown solid **53**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J*=7.2, 6H), 3.03 (d, *J*=23.1, 2H), 3.70 (bs, 2H), 3.95-4.03 (m, 4H), 6.61 (d, *J*=8.4, 2H), 7.15 (dd, *J*=8.5, 2.4, 2H).

The crude aniline **53** and pyridine (4.7 mL, 59 mmol) were dissolved in CH_2Cl_2 and the resulting solution was cooled to approximately 4 °C in an ice-bath. Trifluoroacetic anhydride (5.42 mL, 39 mmol) was then added dropwise while stirring and the resulting solution was stirred for a further 20 h while slowly warming to room temperature. The reaction was quenched by the addition of water (100 ml) and the product was extracted with CH_2Cl_2. The organic extracts were combined and washed with 10% HCl and brine followed by drying over Na_2SO_4. After filtration and concentration, the crude product was purified by flash column chromatography (gradient of 90-100% EtOAc in hexanes) resulting in the colorless solid **60** (9.41 g, 71% yield from 4-

nitrobenzylbromide). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.2, 6H), 3.15 (d, *J*=23.1, 2H), 3.98-4.07 (m, 4H), 7.18 (dd, *J*=8.5, 2.4, 2H), 7.54 (d, *J*=8.4, 2H), 9.98 (s, 1H).

Diethyl (4-(2,2,2-trifluoroacetamido)phenyl)bromomethylphosphonate (55). A solution of **60** (9.41 g, 27.7 mmol), NBS (7.5 g, 41.6 mmol) and azobis(cyclohexane carbonitrile) (70 mg, 0.29 mmol) in benzene was heated to reflux under the presence of a strong visible light for 5 h. After the addition of water the product was extracted with EtOAc. The organics were washed with saturated NaCl then dried over Na_2SO_4. The crude solid was purified by silica gel chromatography on an automated flash purification system (Biotage™) (1:1 EtOAc:hexanes) to give **55** as a pale yellow solid (4.0 g, 34% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, *J*=8.3, 6H), 4.22-4.30 (m, 4H), 4.85, (d, *J*=13.6, 1H), 7.54 (dd, *J*=8.7, 1.7, 2H), 7.60 (d, *J*=8.6, 2H), 8.85 (s, 1H).

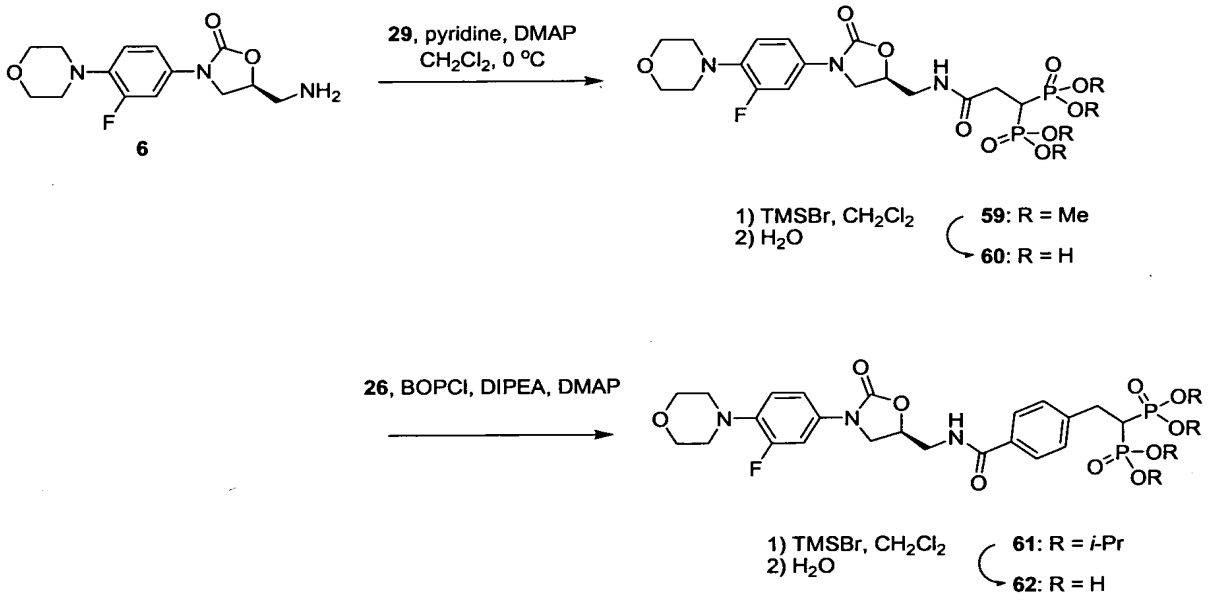
Diethyl (4-(2,2,2-trifluoroacetamido)phenyl)methylbisphosphonate (56). A solution of **55** (4.0 g, 9.6 mmol) and triethylphosphite (1.6 ml, 9.6 mmol) in THF was heated to reflux for 20 h. The solution was cooled to room temperature and concentrated to approximately 5 mL then diethyl ether was added. The product **56** was collected as a colorless precipitate (0.6 g, 14% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, *J*=7.5, 6H), 1.32 (t, *J*=7.5, 6H), 3.7 (t, *J*=24.8, 1H), 3.82-3.92 (m, 2H), 3.96-4.06 (m, 2H), 4.13-4.20 (m, 4H), 7.40 (m, 2H), 7.59 (d, *J*=8.9, 2H), 9.92 (s, 1H).

4-(4-(Di(ethoxyphosphono)methyl)phenylcarbamoyl)butanoic acid (58). A suspension of **56** (0.45 g, 0.95 mmol) and KOH (64 mg, 1.05 mmol) in H_2O was stirred while warming to 50 °C for 5 h. The solution was diluted with H_2O and neutralized with 20 ml saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to the pale yellow solid of **57** (330 mg, 92% crude yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.13 (t, *J*=7.2, 6H), 1.25 (t, *J*=7.2, 6H), 3.59 (t, *J*=25.0, 1H), 3.70 (s, 2H), 3.84-3.94 (m, 4H), 3.97-4.13 (m, 4H), 6.61 (d, *J*=8.5, 2H), 7.20-7.23 (m, 2H).

A solution of crude aniline **57** (330 mg, 0.87 mmol) and glutaric anhydride (109 mg, 0.96 mmol) in CH_2Cl_2 containing a catalytic amount of DMAP was stirred at room temperature for 20 h. The solution was concentrated to dryness and the crude material was purified by silica gel flash column chromatography (gradient of 100% CH_2Cl_2 to CH_2Cl_2/ MeOH, 95:5) resulting in **58** as a colorless solid (430 mg, 100% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, *J*=7.3, 6H), 1.19 (t, *J*=7.3, 6H), 1.75-1.82 (m, 2H), 2.15 (t, *J*=7.7, 2H), 2.30-2.35 (m, 2H), 3.75-3.93 (m, 4H), 4.00-4.06 (m, 4H), 4.20 (t, *J*=25.3, 1H), 7.38 (m, 2H), 7.53 (d, *J*=8.8, 2H), 9.97 (s, 1H).

B-3) Synthesis of Eperezolid- and Linezolid-bisphosphonate conjugates

Scheme 11: Synthesis of linezolid-bisphosphonate conjugates 59-62.



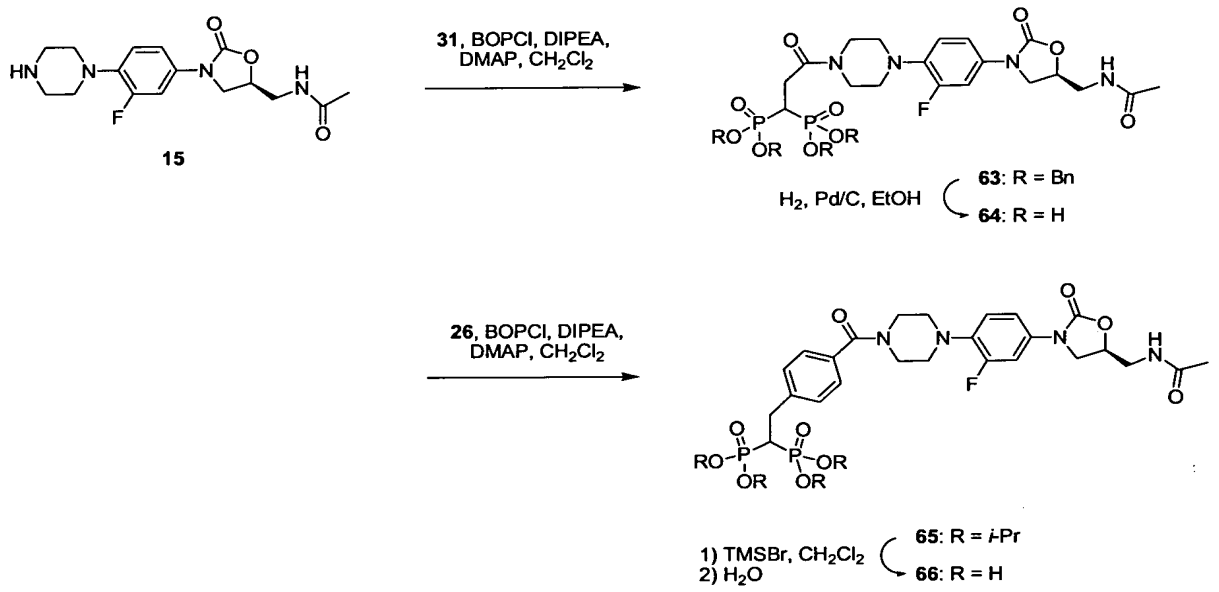
Linezolid tetramethylbisphosphonate 59. To a solution of amine **6** (215 mg, 0.73 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added pyridine (177 µL, 2.19 mmol) followed by a solution of acid chloride **29** (249 mg, 0.80 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at 0 °C for 30 min after which it was diluted with EtOAc (25 mL). The organic layer was washed with H_2O (10 mL) and saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude **59** was purified by flash chromatography using a gradient of 0-2-5% MeOH / $CHCl_3$ as eluent. Evaporation of combined pure fractions yielded **59** as a pink solid (179 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$ + 1 drop CD_3OD) δ 2.70 (td, *J*=16.2, 6.5, 2H), 3.04-3.06 (m, 4H), 3.24 (tt, *J*=23.7, 6.5, 1H), 3.40-3.60 (m, 1H), 3.64-3.70 (m, 1H), 3.72-3.82 (m, 13H), 3.86-3.90 (m, 4H), 3.99 (t, *J*=8.8, 1H), 4.71-4.77 (m, 1H), 6.96-7.00 (m, 1H), 7.08-7.11 (m, 1H), 7.43 (dd, *J*=14.3, 2.3, 1H). LCMS : 98.1% (254 nm), 97.0% (220 nm), 91.4% (320 nm). MS : 568.1 $(MH)^+$.

Linezolid bisphosphonic acid 60. To a solution of phosphonate **59** (86 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added TMSBr (200 µL, 1.52 mmol). The reaction mixture was stirred for 48 h after which it was concentrated to dryness. H_2O (3 mL) was added, the reaction mixture was stirred for 1 h and concentrated to dryness to afford 77 mg (quant.) of **60** as a pink solid. ^{1}H NMR (400 MHz, D_2O) δ 2.53-2.67 (m, 3H), 3.49 (d, *J*=4.7, 2H), 3.52 (t, *J*=4.9, 4H), 3.74 (dd, *J*=9.4, 6.3, 1H), 3.95 (t, *J*=4.5, 4H), 4.08 (t, *J*=9.2, 1H), 4.75-4.81 (m, 1H), 7.22-7.25 (m, 1H), 7.47 (d, *J*=8.8, 1H), 7.51 (dd, *J*=13.9, 2.4, 1H).

Linezolid tetraisopropylbisphosphonate 61. To a solution of acid **26** (668 mg, 1.35 mmol) in CH_2Cl_2 (14 mL) were added diisopropylethylamine (472 μL, 2.71 mmol), DMAP (8 mg) and bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOPCl, 690 mg, 2.71 mmol). The solution turned yellow after stirring for 15 min and a solution of amine **6** (400 mg, 2.71 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 16 h, after which it was diluted with EtOAc (100 mL) and washed with saturated NH_4Cl solution (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), the combined organic layers were washed with brine (25 mL), dried overNa_2SO_4, filtered and concentrated under reduced pressure. Crude amide **61** was purified by flash chromatography using a gradient of 0-3% MeOH / CH_2Cl_2 to afford **61** as a white solid (242 mg, 24% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.32 (m, 24H), 4.49 (tt, *J*=24.1, 6.4, 1H), 3.02-3.05 (m, 4H), 3.24 (td, *J*=16.4, 6.1, 2H), 3.77-3.82 (m, 2H), 3.85-3.87 (m, 4H), 3.90-3.97 (m, 1H), 4.07 (t, *J*=9.0, 1H), 4.71-4.79 (m, 4H), 4.85-4.89 (m, 1H), 6.58 (t, *J*=6.3, 1H), 6.92 (t, *J*=8.9, 1H), 7.07 (dd, *J*=9.1, 2.4, 1H), 7.36 (d, *J*=8.3, 2H), 7.44 (dd, *J*=14.2, 2.6, 1H), 7.68 (d, *J*=8.3, 2H). LCMS : 93.4% (254 nm), 96.8% (220 nm), 100% (320 nm). MS : 756.3 $(MH)^+$.

Linezolid bisphosphonic acid 62. Following the same protocol as for **60**, bisphosphonate **61** (101 mg, 0.13 mmol) was deprotected to provide diphosphonic acid **62** as a white solid (98 mg, quant.). ^{1}H NMR (400 MHz, D_2O) δ 2.52 (tt, *J*=22.8, 6.2, 1H), 3.14 (td, *J*=16.6, 6.6, 2H), 3.56-3.58 (m, 4H), 3.73 (dd, *J*=14.6, 3.0, 1H), 3.80 (dd, *J*=14.6, 4.3, 1H), 3.95 (dd, *J*=9.3, 5.0, 1H), 4.03-4.05 (m, 4H), 4.23 (t, *J*=8.9, 1H), 4.95-5.01 (m, 1H), 7.22-7.25 (m, 1H), 7.32 (d, *J*=8.0, 2H), 7.47-7.53 (m, 4H).

Scheme 12. Synthesis of bisphosphonate conjugatesof N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide (63-66).



N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide tetrabenzylbisphosphonate conjugate 63. Acid **31** (100 mg, 0.168 mmol) was coupled with amine **15** (57 mg, 0.168 mmol) using the same protocol as for **61.** The crude mixture was purified by flash chromatography using 10% EtOH / EtOAc to afford **63** as a white solid (98 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.77-2.90 (m, 5H), 3.47 (s, 2H), 3.61 (dt, *J*=14.8, 6.1, 1H), 3.69-3.81 (m, 6H), 4.02 (t, *J*=9, 1H), 4.77 (m, 1H), 4.96-5.01 (m, 8H), 5.92 (t, *J*=6.3, 1H), 6.8 (t, 1H), 7.08 (d, 1H), 7.3 (s, 20 H), 7.43 (d, *J*=13.3, 1H).

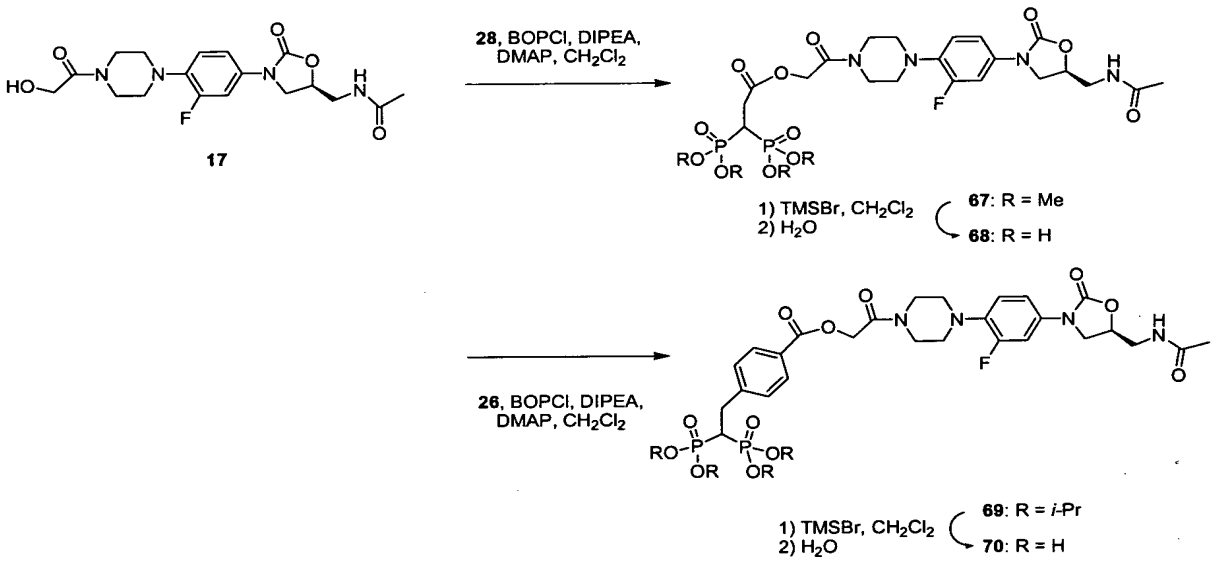
N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide bisphosphonic acid conjugate 64. A solution of compound **63** (100 mg, 0.11 mmol) in EtOH (25 mL) was placed in a Parr vessel and treated with 10% Pd / C (10 mg). The solution was shaken under 60 psi of H_2 for 30 min. The solution was filtered on Celite and concentrated under vacuum to give bisphosphonic acid **64** as a white solid (57 mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (s, 3H), 2.7 (m, 3H), 2.9 (s, 2H), 3.0 (s, 2H), 3.4 (m, 2H), 3.57 (s, 4H), 3.65 (t, *J*= 8.4, 1H), 4.04 (t, *J*= 9.0, 1H), 4.65 (m, 1H), 7.05 (t, *J*= 10.6, 1H), 7.15 (d, *J*= 8.6, 1H), 7.45 (d, *J*= 14.5,1H), 8.2 (m, 1H).

N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide tetraisopropylbisphosphonate conjugate 65. Acid **26** (150 mg, 0.31 mmol) was coupled with amine **15** (105 mg, 0.31 mmol) using the same protocol as for **61.** Crude product was purified by flash chromatography using 10% EtOH / EtOAc to afford amide **65** as a colorless oil (184 mg,

75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (m, 24H), 2.02 (s, 3H), 2.51 (tt, *J*= 24, 6.26, 1H), 2.90-3.11 (m, 4H), 3.25 (dt, *J*= 16.6, 6.0, 2H), 3.57-3.81 (m, 6H), 3.85-4.05 (m, 2H), 4.75 (m, 5H), 5.95 (t, *J*= 6.1, 1H), 6.92 (t, *J*= 14, 1H), 7.17 (d, *J*= 9, 1H), 7.37 (s, 4H), 7.45 (d, *J*= 14, 1H).

N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxo-oxazolidin-5-yl)methyl)acetamide bisphosphonic acid conjugate 66. Following the same protocol as for **60**, bisphosphonate **65** (180 mg, 0.225 mmol) was deprotected to provide diphosphonic acid **66** as a pink solid (102 mg, 77%). ^{1}H NMR (400 MHz, D_2O) δ 1.80 (s, 3H), 2.45-2.57 (m, 1H), 3.10 (s, 4H), 3.23 (s, 2H), 3.38 (s, 2H), 3.45 (m, 2H), 3.59 (s, 2H) 3.7 (m, 1H), 3.90 (s, 2H), 4.05 (t, *J*= 9.2, 1H), 4.75 (m, 1H), 7.17 (d, *J*= 8.8, 1H), 7.2 (t, *J*= 9.0, 1H), 7.27 (d, *J*= 8.0, 2H), 7.32 (d, *J*= 8.0, 2H), 7.36 (s, 1H).

Scheme 13. Synthesis of eperezolid-bisphosphonate conjugates 67-70.



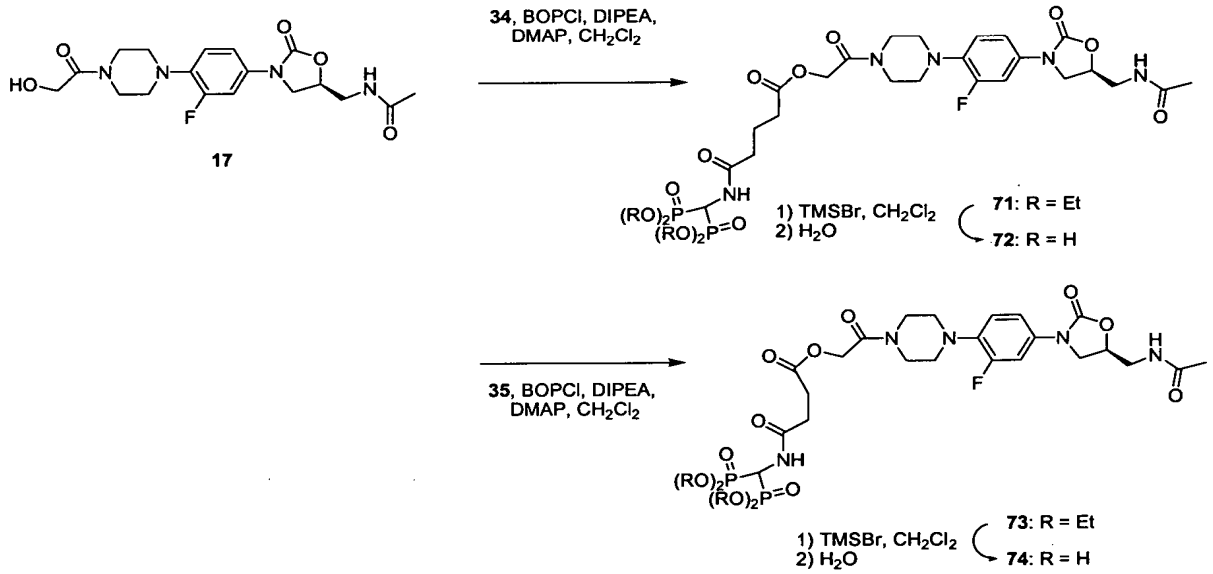
Eperezolid tetramethylbisphosphonate 67. Acid **31** (60 mg, 0.21 mmol) was coupled with alcohol **17** (83 mg, 0.21 mmol) using the same protocol as for **61**. The crude mixture was purified by flash chromatography using 15% MeOH / CH_2Cl_2 to afford ester **67** as a white solid (30 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.95-3.22 (m, 6H), 3.55-3.87 (m, 20H), 4.03 (t, *J*= 9.0, 1H), 4.20 (s, 1H), 4.73-4.78 (m, 1H), 4.80 (s, 1H), 6.25 (m, 1H), 6.91 (t, *J*= 9.0, 1H), 7.06 (d, *J*= 9.0, 1H), 7.46 (d, *J*= 14.3, 1H).

Eperezolid bisphosphonic acid 68. Following the same protocol as for **60**, bisphosphonate **67** (30 mg, 0.045 mmol) was deprotected to provide diphosphonic acid **68** as a pink solid (27 mg, quant.). ^{1}H NMR (400 MHz, D_2O) δ 1.81 (s, 3H), 2.62-2.90 (m, 3H), 3.43 (t, *J*= 4.9, 1H), 3.47 (s, 2H), 3.53 (s, 2H), 3.68 (m, 1H), 3.79 (m, 3H), 4.06 (t, *J*= 9.2, 1H), 4.25 (s, 1H), 4.73-4.76 (m, 1H), 4.85 (s, 1H), 7.19 (d, *J*= 9.0, 1H), 7.42 (t, *J*= 9.0, 1H), 7.48 (d, *J*= 13.9, 1H).

Eperezolid tetraisopropylbisphosphonate 69. Acid **26** (100 mg, 0.21 mmol) was coupled with alcohol **17** (83 mg, 0.21 mmol) using the same protocol as for **61**. The crude mixture was purified by flash chromatography using 5% EtOH / EtOAc to afford ester **69** as a white solid (60 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21-1.30 (m, 24H), 1.99 (s, 3H), 2.51 (tt, *J*= 24, 6.2, 1H), 3.03 (m, 2H), 3.07 (m, 2H), 3.23 (td, *J*= 16.6, 6.3, 2H), 3.43 (m, 1H), 3.56-3.65 (m, 3H), 3.73-3.83 (m, 3H), 4.01 (t, *J*= 8.8, 1H), 4.20 (s, 1H), 4.70-4.78 (m, 5H), 4.98 (s, 1H), 6.53 (m, 1H), 6.87-6.93 (m, 1H), 7.06 (d, *J*= 8.8, 1H), 7.35 (d, *J*= 8.4, 2H), 7.45 (d, *J*= 14.1, 1H), 7.98 (d, *J*= 8.4, 2H).

Eperezolid bisphosphonic acid 70. Following the same protocol as for compound **60**, bisphosphonate **69** (50 mg, 0.058 mmol) was deprotected to provide diphosphonic acid **70** as a white solid (37 mg, 92%). ^{1}H NMR (400 MHz, D_2O) δ 1.86 (s, 3H), 2.20 (t, *J*= 8.1, 1H), 2.99-3.12 (m, 6H), 3.41-3.51 (m, 2H), 3.63 (s, 4H), 3.69 (t, *J*= 9.1, 1H), 4.1 (t, *J*= 9.0, 1H), 4.76 (m, 1H), 5.03 (s, 2H), 7.09 (m, 2H), 7.28-7.31 (d, *J*= 14.0, 1H), 7.38 (d, *J*= 7.6, 2H), 7.88 (d, *J*= 7.6, 2H). MS : 685.0 (M-H).

Scheme 14. Synthesis of eperezolid-bisphosphonate conjugates 72 and 74.



Eperezolid tetraethylbisphosphonate 71. To a solution of acid **34** (1.27 g, 3.04 mmol), alcohol **17** (1.024 g, 2.60 mmol) and diisopropylethylamine (1.13 mL, 6.5 mmol) in CH_2Cl_2 (60 mL) were added bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOPCl, 0.793 g, 3.12 mmol) and a catalytic quantity of DMAP. The reaction mixture was stirred 26 h, and then evaporated onto SiO_2 (6 g). The crude mixture was purified twice by flash chromatography using a gradient of 10-20% MeOH / CH_2Cl_2 to afford **71** as a white solid (1.23 g, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$)

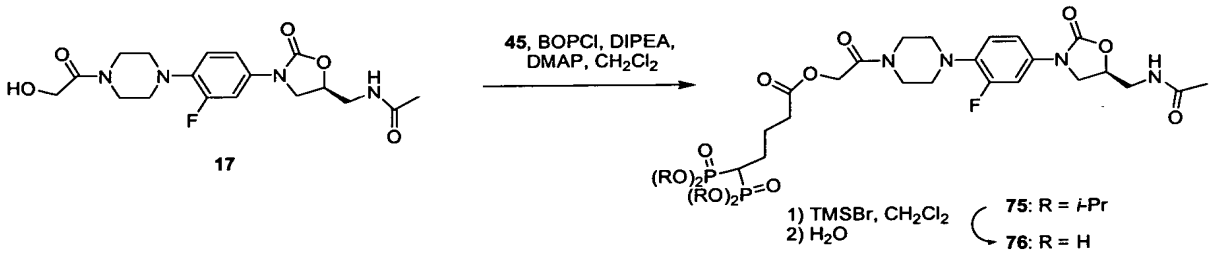
δ 1.24-1.35 (m, 12H), 2.02 (s, 3H), 2.00-2.08 (m, 2H), 2.45 (t, *J*=6.9, 2H), 2.52 (t, *J*=6.7, 2H), 3.01-3.11(m, 4H), 3.43-3.86 (m, 7H), 4.02 (t, *J*=9.0, 1H), 4.06-4.21 (m, 8H), 4.73-4.80 (m, 1H), 4.82 (s, 2H), 5.10 (td, *J*=21.9, 10.1, 1H), 6.03 (t, *J*=6.3, 1H), 6.91 (t, *J*=9.0, 1H), 7.06-7.16 (m, 2H), 7.45-7.49 (m, 1H). MS : 794.3 $(MH)^+$.

Eperezolid bisphosphonic acid 72. To a solution of phosphonate **71** (2.40 g, 3.024 mmol) in CH_2Cl_2 (50 mL) was added TMSBr (4 mL, 30.3 mmol). The reaction mixture was stirred for 14 h after which it was concentrated to dryness. The residue was taken up in deionised water (200 mL) and the pH immediately adjusted to 7.4 with 1M NaOH. EtOAc (50 mL) was added, the mixture cooled to 0 °C, and carefully basified to pH 9.1 with Na_2CO_3. The phases were separated, and the aqueous extracted with ethyl acetate (3 x 50 mL), neutralised with 1M HCl and concentrated to dryness to afford **72** as a white solid (2.24 g, 96% yield, assuming the product is the tetrasodium salt). ^1H NMR (400 MHz, D_2O) δ 1.94-2.06 (m, 2H), 2.00 (s, 3H), 2.42 (t, *J*=7.7, 2H), 2.61 (t, *J*=7.4, 2H), 3.08-3.18 (m, 4H), 3.54-3.86 (m, 7H), 4.15-4.30 (m, 2H), 4.87-4.93 (m, 1H), 4.97 (s, 2H), 7.18-7.24 (m, 2H), 7.41-7.45 (m, 1H). MS : 680.1 (M-H).

Eperezolid tetraethylbisphosphonate 73. Acid **35** (0.2063 g, 0.512 mmol) was coupled with alcohol **17** (0.2052 g, 0.520 mmol) using the same protocol as for **71**. The crude mixture was purified twice by flash chromatography using a gradient of 10-20% MeOH / CH_2Cl_2 to afford **73** as a white solid (0.1637 g, 41% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 1.30-1.36 (m, 12H), 2.02 (s, 3H), 2.65 (t, *J*=6.9, 2H), 2.81 (t, *J*=6.8, 2H), 3.03-3.06(m, 4H), 3.43-3.85 (m, 7H), 4.01 (t, *J*=8.9, 1H), 4.17-4.25 (m, 8H), 4.74-4.77 (m, 1H), 4.79 (s, 2H), 5.01 (td, *J*=21.6, 10.2, 1H), 6.18 (t, *J*=6.2, 1H), 6.37 (d, *J*=10.0, 1H), 6.90 (t, *J*=9.1, 1H), 7.45-7.49 (m, 1H).

Eperezolid bisphosphonic acid 74. Following the same protocol as for compound **72**, bisphosphonate **73** (0.5011 g, 0.643 mmol) was deprotected to provide diphosphonic acid **74** as a white solid in quantitative yield. The crude material was purified by reverse phase chromatography to give 240 mg (49% recovery, assuming the product is the tetrasodium salt). ^1H NMR (400 MHz, D_2O) δ 2.00 (s, 3H), 2.71-2.74 (m, 2H), 2.82-2.85 (m, 2H), 3.10-3.18 (m, 4H), 3.55-3.85 (m, 7H), 4.18-4.39 (m, 2H), 4.88-4.94 (m, 1H), 4.99 (s, 2H), 7.18-7.25 (m, 2H), 7.41-7.45 (m, 1H). MS : 668.1 $(MH)^+$.

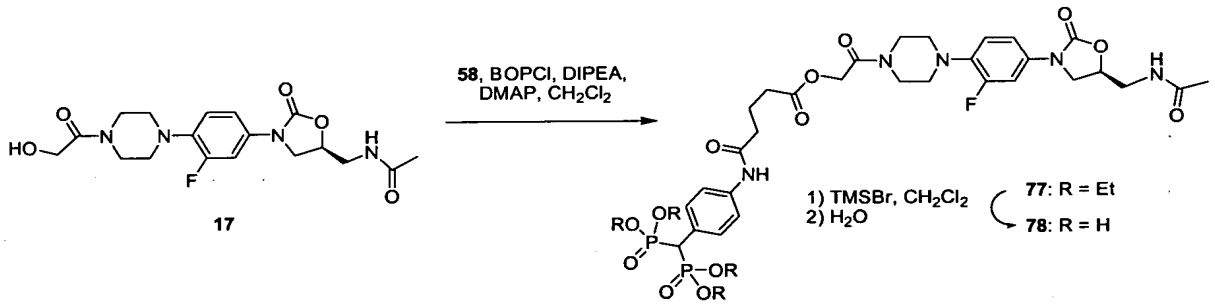
Scheme 15. Synthesis of eperezolid-bisphosphonate conjugate 70.



Eperezolid tetraisopropylbisphosphonate (75). Acid **45** (235 mg, 0.546 mmol) was coupled with eperezolid (215 mg, 0.545 mmol) in the presence of BOPCl (289 mg, 1.10 mmol), DIPEA (0.20 mL, 1.15 mmol) and a catalytic amount of DMAP in 3 mL of dichloromethane. After stirring overnight at room temperature, the mixture was concentrated and subjected to flash chromatography eluting with 20:1 CH_2Cl_2:MeOH. The obtained impure product was then applied to a WATERS C18 sep-pak™ (12 cc) with gradient solvent of 18 mL water, 18 mL 2:1water:MeOH, 18 mL 1:2 water:MeOH and 18 mL methanol. The pure product **75** was obtained as a pale yellow oil (220 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.36 (m, 24H), 1.90-2.00 (m, 4H), 2.02 (s, 3H), 2.15 (tt, *J* = 24.4, 5.9, 1H), 2.48 (t, *J* = 6.9, 2H), 3.04-3.07 (m, 4H), 3.56-3.78 (m, 7H), 4.02 (t, *J* = 9.0, 1H), 4.74-4.83 (m, 7H), 5.95 (t, *J* = 6.3, 1H), 6.92 (t, *J* = 9.0, 1H), 7.08 (dd, *J* = 8.8, 2.6, 1H), 7.47 (dd, *J* = 13.1, 2.5, 1H).

Eperezolid bisphosphonic acid (76). Product bisphosphonic acid **76** was obtained by treating 60 mg (0.07437 mmol) of compound **75** with 0.50 mL (3.713 mmol) of bromotrimethylsilane in 1 mL of dichloromethane. After reaction was complete as monitored by ^{1}H NMR, the solvent was removed and the residue was taken up in water and concentrated on a rotary evaporator (3 x) followed by neutralization to pH = 7.09 with 0.50M NaOH. The pure form of the final product (8.8 mg, 19%) was obtained by passing the crude material through semi-preparative reverse phase HPLC. ^{1}H NMR (400 MHz, D_2O) δ 1.76-1.90 (m, 5H), 1.99 (s, 3H), 2.56 (t, *J* = 7.0, 2H), 3.10-3.17 (m, 4H), 3.54-3.76 (m, 6H), 3.82 (dd, *J* = 9.4, 5.9, 1H), 4.22 (t, *J* = 9.2, 1H), 4.88-4.91 (m, 1H), 4.95 (s, 2H), 7.17-7.24 (m, 2H), 7.41-7.45 (m, 1H); ^{31}P NMR (162 MHz, D_2O): δ20.87 (s); ^{19}F NMR (376 MHz, D_2O) δ-121.49 (dd, *J* = 13.2, 7.5); MS: 637 (M-H).

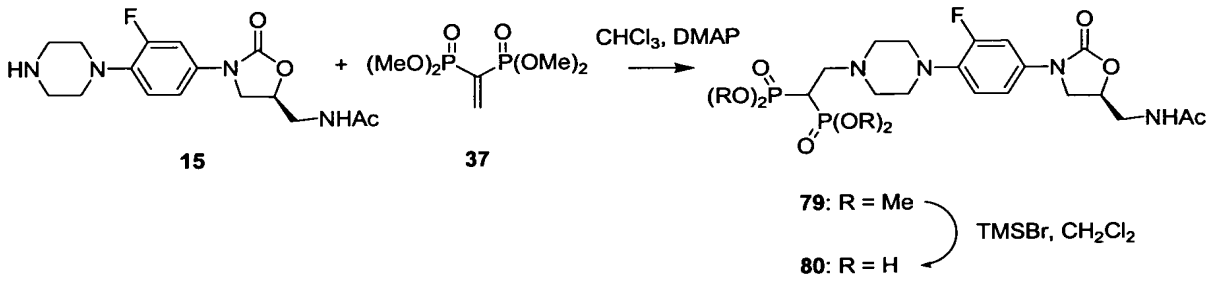
Scheme 16. Synthesis of eperezolid-bisphosphonate conjugate 78.



4-(4-(Di(ethoxyphosphono)methyl)phenylcarbamoyl)butanoyl eperezolid (77). To a solution of **58** (430 mg, 0.871 mmol) in CH_2Cl_2 (10 mL) were added diisopropylethylamine (304 µL, 2.71 mmol), DMAP (3 mg) and bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOPCl, 333 mg, 1.31 mmol). After stirring for 10 min eperezolid (344 mg, 0.871 mmol) was added in one portion. The mixture was stirred for 18 h, after which the solvent was removed under reduced pressure. Crude product was purified by flash chromatography (gradient of 0-30% MeOH / EtOAc) to afford **77** as a pale yellow solid (434 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, *J*=7.2, 6H), 1.29 (t, *J*=7.2, 6H), 2.02 (s, 3H), 2.11-2.18 (m, 2H), 2.46-2.55 (m, 4H), 3.08-3.16 (m, 4H), 3.57-3.65 (m, 6H), 3.83-3.98 (m, 4H), 4.00-4.17 (m, 7H), 4.74-4.81 (m, 1H), 4.89 (s, 2H), 6.09 (t, *J*=5.9,1H), 6.95 (t, *J*=9.5,1H), 7.09 (dd, *J*=8.8, 2.2, 1H), 7.37-7.42 (m, 2H), 7.50 (dd, *J*=14.1, 2.2, 1H), 7.59 (d, *J*=8.7, 2H), 9.33 (s, 1H). LCMS: 94.9% (254 nm), 95.4% (220 nm), N/A (320 nm). MS: (MH^+) 870.3.

Eperezolid bisphosphonic acid (78). TMSBr (1.15 mL, 8.74 mmol) was added in one portion to a stirring solution of **77** (380 mg, 0.437 mmol) in CH_2Cl_2 and the resulting mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and solid was dried under high vacuum for 1 h. The solid was then re-suspended in H_2O and the pH was adjusted to pH 7 by the addition of 1M NaOH. The solution was concentrated to half volume then subjected to purification by WATERS C18 sep-pak™ (gradient of 0-10% MeOH / H_2O) to give the colorless solid **78** (150 mg, 45% yield). ^{1}H NMR (400 MHz, D_2O) δ 1.84 (s, 3H), 1.86-1.93 (m, 2H), 2.36 (t, *J*=7.6, 2H), 2.47 (t, *J*=7.6, 2H), 2.94 (bt, *J*=4.8, 2H), 3.01 (bt, *J*=4.8, 2H), 3.30 (t, *J*=21.7, 1H), 3.39-3.50 (m, 2H), 3.53 (bt, *J*=4.8, 2H), 3.60 (bt, *J*=4.8, 2H), 3.68 (dd, *J*=9.7, 6.0, 1H), 4.06 (t, *J*=4.1, 1H), 7.72-4.78 (m, 1H), 4.81 (s, 2H), 7.02-7.09 (m, 2 H), 7.2 (d, *J*=7.6, 2H), 7.26-7.32 (m, 3H), LCMS: 96.8% (254 nm), 97.2% (220 nm), N/A (320 nm). MS: (MH^-) 756.2.

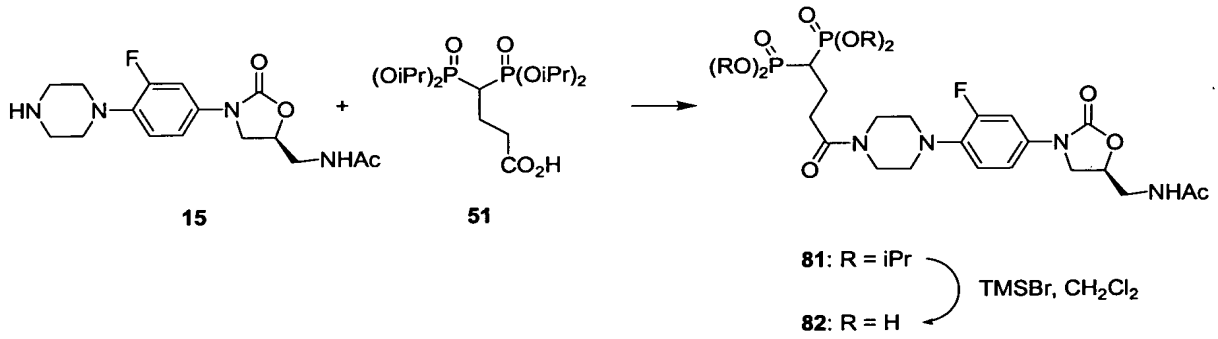
Scheme 17. Synthesis of N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 80.



N-(((S)-3-(3-fluoro-4-(4-(2,2-bis(dimethylphosphono)ethyl)-piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (79).). A solution of amine **15** (0.50 g, 1.50 mmol), alkene **37** (0.37 g, 1.52 mmol) and one crystal of DMAP in anhydrous $CHCl_3$ (45 mL) was stirred at room temperature overnight. Evaporation of the mixture gave essentially pure **79** as a sticky foam in quantitative yield, which was used in the next step. Recrystallization of a portion of this material from toluene gave pure **79** as white crystals with a recovery of 25%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.64-2.71 (m, 4H), 2.72 (tt, *J*=23.5, 6.5, 1H), 2.96 (td, *J*=14.6, 6.5, 2H), 3.02-3.10 (m, 4H), 3.56-3.76 (m, 3H), 3.83 (dd, *J*=11.2, 4.3, 12H), 4.01 (t, *J*=9.0, 1H), 4.73-4.79 (m, 1H), 6.05 (t, *J*=6.2,1H), 6.90 (t, *J*=9.1, 1H), 7.05 (dd, *J*=8.8, 2.3, 1H), 7.42 (dd, *J*=14.4, 2.6, 1H).

N-(((S)-3-(3-fluoro-4-(4-(2,2-bisphosphonoethyl)-piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (80). TMSBr (1.05 mL, 7.9 mmol) was added in one portion to a stirring solution of **79** (460 mg, 0.79 mmol) in anhydrous CH_2Cl_2 (50 mL) and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated and the residue stirred in water for a few hours. This solution was evaporated to dryness. A portion of the resulting solid was treated with aqueous sodium acetate and the resulting (presumably bis) sodium salt precipitated with ethanol. The salt was subjected to purification by WATERS C18 sep-pak eluting with water to give **80** as a colourless solid (0.072 g, 61% recovery from sep-pak purification). ^{1}H NMR (400 MHz, D_2O) δ 1.99 (s, 3H), 2.32-2.48 (m, 1H), 3.20-3.70 (m, 13H), 3.81 (dd, *J*=9.4, 5.9, 1H), 4.19 (t, *J*=9.2, 1H), 4.85-4.95 (m, 1H), 7.16-7.24 (m, 2H), 7.41 (dd, *J*=14.0, 2.2, 1H).

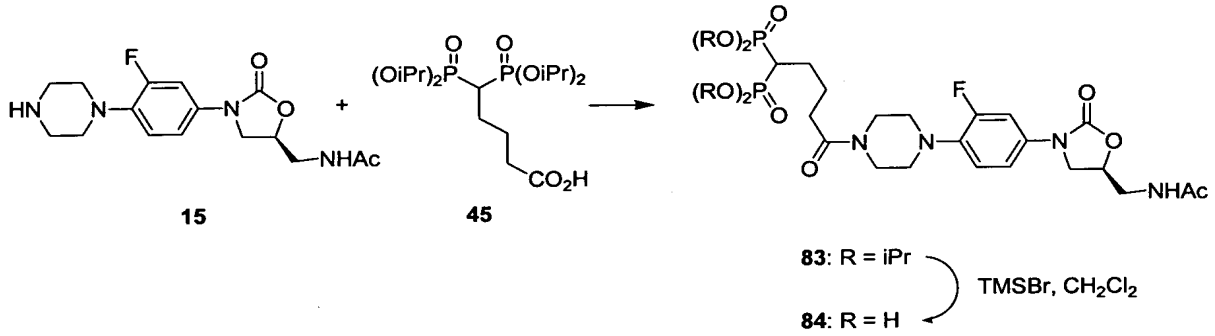
Scheme 18. Synthesis of N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 82.



N-(((S)-3-(3-fluoro-4-(4-(4,4-bis(diisopropylphosphono)butyryl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (81). Acid **51** (246.5 mg, 0.5920 mmol) in dichloromethane (4 mL) was treated with DMAP (one crystal), DIPEA (0.21 mL, 1.206 mmol) and BOPCl (234.4 mg, 0.8931 mmol) at room temperature for 30 min and Compound **15** (199.3 mg, 0.5925 mmol) was added. The mixture was stirred overnight before being concentrated. The residue was applied to flash chromoatography on silica gel with the elution of 20:1 (v/v) dichloromethane/methanol then 10:1 to yield the product **81** (243 mg, 56 %) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 6.2, 24H), 2.03 (s, 3H), 2.16-2.30 (m, 2H), 2.35 (tt, *J* = 24.1, 6.3, 1H), 2.75 (t, *J* = 7.7, 2H), 2.99-3.04 (m, 4H), 3.59-3.78 (m, 7H), 4.02 (t, *J* = 8.8, 1H),4.74-4.83 (m, 5H), 6.19 (t, *J* = 6.1, 1H), 6.90 (t, *J* = 8.8, 1H), 7.08 (dd, *J* = 9.0, 2.6, 1H), 7.46 (dd, *J* = 14.1, 2.4, 1H).

N-(((S)-3-(3-fluoro-4-(4-(4,4-bisphosphonobutyryl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (82). Compound **81** (117 mg, 0.1592 mmol) in dichloromethane (2 mL) was treated with 1.07 mL (7.945 mmol) of TMSBr for 24 h at rt. After concentration, the residue was taken up in small amount of water and the solvent was evaporated. The process was repeated twice and the residual material was dissolved in small amount water. The solution was neutralized to pH = 7 with 0.5 M NaOH and concentrated again. The material was applied to a semi-preparative HPLC column (XTerra® Prep RP_{18}, 10 μm, 10x300 mm) with gradient elution from water to methanol to afford product **82** (9 mg, 10 %) as a white powder. ^{1}H NMR (400 MHz, D_2O) δ 1.84 (tt, *J* = 20.7, 6.4, 1H), 1.99 (s, 3H), 2.00-2.14 (m, 2H), 2.73-2.78 (m, 2H), 3.08 (bs, 2H), 3.17 (bs, 2H), 3.54-3.64 (m, 2H), 3.75 (bs, 2H), 3.83 (bs, 3H), 4.16-4.25 (m, 1H), 4.86-4.92 (m, 1H), 7.16-7.24 (m, 2H), 7.42 (d, *J* = 14.1, 1H); ^{31}P NMR (162 MHz, D_2O) δ 20.20; ^{19}F NMR (376 MHz, D_2O) δ -121.38 (dd, *J* = 13.8, 8.6); MS: 565(M-H).

Scheme 19. Synthesis of N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 84.

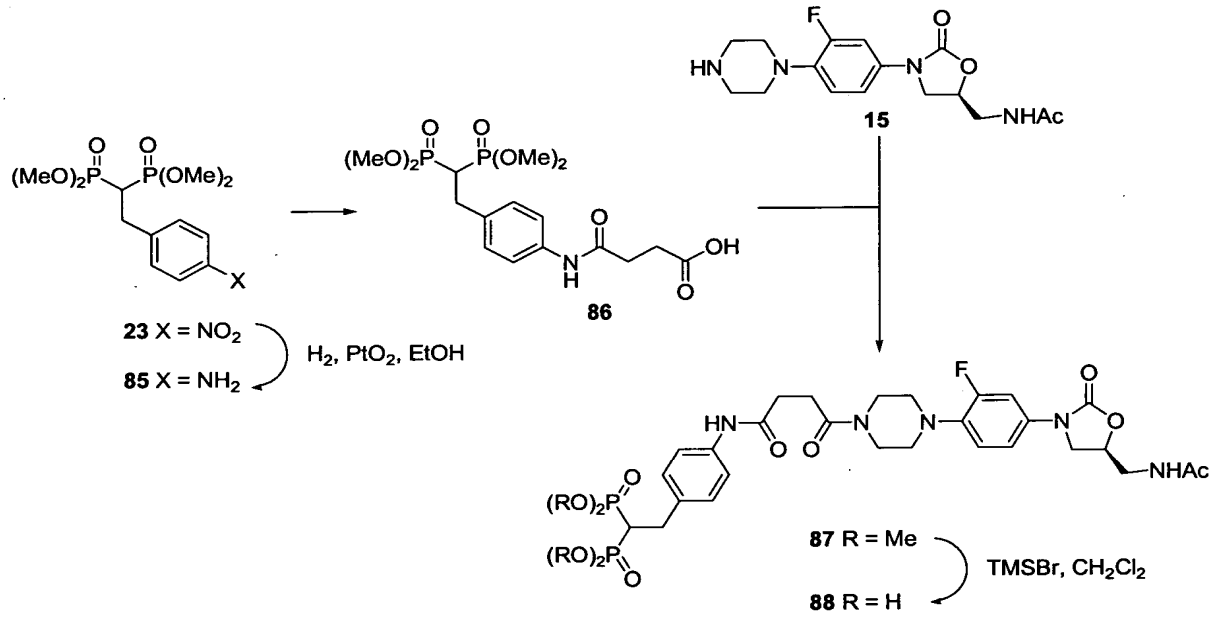


N-(((S)-3-(3-fluoro-4-(4-(5,5-bis(diisopropylphosphono)pentanoyl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (83). Acid **45** (234.9 mg, 0.5458 mmol), BOPCl (215.1 mg, 0.8196 mmol), DIPEA (0.20 mL, 1.148 mmol) and DMAP (a few crystals) were mixed in 4 mL of anhydrous dichloromethane and the white suspension was stirred at room temperature for 30 min. Compound **15** (184.1 mg, 0.5473 mmol) was then added and the yellow suspension was stirred overnight at room temperature. When the reaction was complete as indicated by TLC, the mixture was diluted with ethyl acetate and quenched with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate (3x) and the combined organic layer was dried over sodium sulfate. Flash chromatography of the concentrated material on silica gel with the elution of 20:1 (v/v) dichloromethane/methanol then 10:1 afforded product **83** (173 mg, 42 %) as a yellow sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.38 (m, 24H), 1.90-1.98 (m, 4H), 2.02 (s, 3H), 2.17 (tt, *J* = 24.1, 6.3, 1H), 2.38 (t, *J* = 7.7, 2H), 2.96-3.04 (m, 4H), 3.60-3.80 (m, 7H), 4.02 (t, *J* = 9.0, 1H), 4.74-4.83 (m, 5H), 6.00 (t, *J* = 6.1, 1H), 6.91 (t, *J* = 9.2, 1H), 7.06-7.10 (m, 1H), 7.46 (dd, *J* = 13.9, 2.4, 1H).

N-(((S)-3-(3-fluoro-4-(4-(5,5-bisphosphonopentanoyl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (84). Compound **83** (113.5 mg, 0.1516 mmol) in 2 mL of dichloromethane was treated with 1.02 mL (7.574 mmol) of TMSBr and the mixture was stirred vigorously at room temperature for 4 days. After concentration, the residue was taken up in small amount of water and the solvent was evaporated. The process was repeated twice. At the end, the material was dissolved in water and the solution was carefully neutralized to pH = 7 with 0.5 M NaOH (aq). The product **84** (15 mg, 17 %) was isolated from a semi-preparative HPLC column (XTerra® Prep RP_{18}, 10 μm, 10x300 mm) with gradient elution from water to methanol as a white powder. ^{1}H NMR (400 MHz, D_2O) δ 1.80-1.94 (m, 5H), 1.99 (s, 3H), 2.53 (t, *J* = 6.9, 2H), 3.08

(bs, 2H), 3.15 (bs, 2H), 3.54-3.65 (m, 2H), 3.73-3.84 (m, 5H), 4.18-4.25 (m, 1H), 4.86-4.94 (m, 1H), 7.17-7.24 (m, 2H), 7.38-7.45 (m, 1H); ^{31}P NMR (162 MHz, D_2O) δ 21.11; ^{19}F NMR (376 MHz, D_2O) δ -121.40 (dd, *J* = 13.6, 8.6); MS: 579(M-H).

Scheme 20. Synthesis of N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 88.



Dimethyl 2-(4-aminophenyl)-1-(dimethylphosphoryl)ethylphosphonate (85). A mixture of **23** (1.01 g, 2.75 mmol) and PtO_2 (0.035 g, 0.15 mmol) in EtOH (40 mL, 95%) was shaken in a PARR apparatus under 55 p.s.i of H_2 for 14 hr. The catalyst was removed by filtration through glass fiber filter paper and the solvent was removed under reduced pressure to give **85** as a pale yellow solid (0.959 g, 103%) that was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (tt, *J*=6.3, 23.9, 1H), 3.12 (dt, *J*=6.3, 16.2, 2H), 3.70 (d, *J*=1.9, 6H), 3.73 (d, *J*=1.9, 6H), 6.61 (d, *J*=8.5, 2H), 7.04 (d, *J*=8.5, 2H).

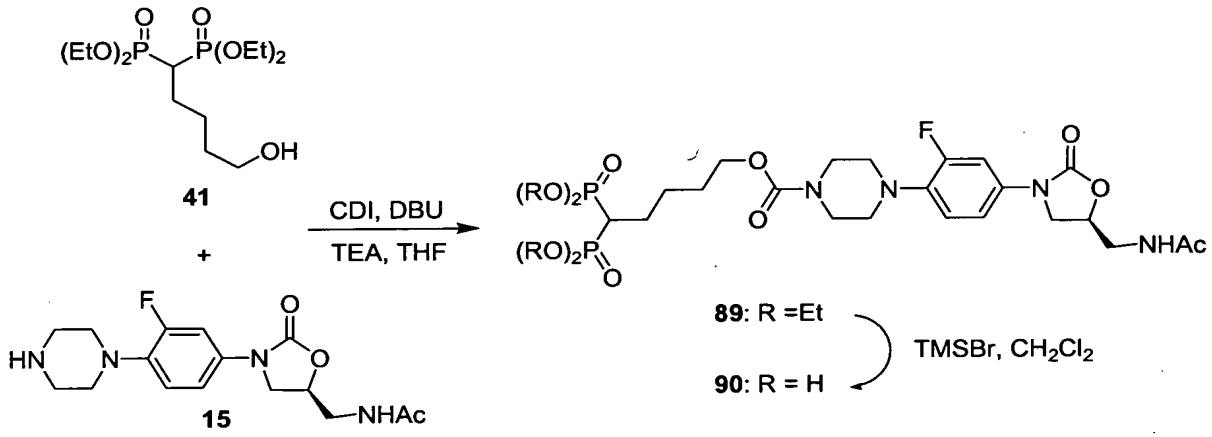
Dimethyl 2-(4-(3-carboxypropionylamino)phenyl)-1-(dimethylphosphoryl)ethylphosphonate (86). A solution containing **85** (334 mg, 0.990 mmol), succinic anhydride (109 mg, 1.09 mmol) and DMAP (10 mg, 0.10 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 48 hr. The solvent was removed under reduced pressure and the crude product was purified by WATERS C18 sep-pak™ chromatography (10% to 20% MeOH in H_2O) resulting in **86** as a colourless solid (210 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

2.65-2.69 (m, 2H), 2.72-2.81 (m, 3H), 3.20 (dt, *J*=6.7, 16.8, 2H), 3.70 (d, *J*=2.0, 6H), 3.73 (d, *J*=2.0, 6H), 7.19 (d, *J*=8.8, 2H), 7.43 (d, *J*=8.8, 2H), 8.00 (bs, 1H).

N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 87. To a solution of **15** (210 mg, 0.480 mmol) and **86** (199 mg, 0.504 mmol) in dry CH_2Cl_2 (5 mL) were added diisopropylethylamine (125 µL, 0.720 mmol), DMAP (4 mg) and bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOPCl, 126 mg, 0.480 mmol). The resulting mixture was stirred at room temperature for 16 hr at which time the reaction appeared to be completed by TLC. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography on an automated flash chromatography system (Biotage™) (0% to 20% MeOH in CH_2Cl_2) to give **87** as a pale yellow solid (305 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.61 (tt, *J*=6.0, 24.1, 1H), 2.67-2.78 (m, 4H), 2.97-3.21 (m, 8H), 3.47 (s, 2H), 3.58-3.67 (m, 2H), 3.69 (s, 6H), 3.72 (s, 6H), 3.78-3.79 (m, 1H), 4.00 (t, *J*=9.0, 1H), 4.72-4.79 (m, 1H), 6.40 (bt, *J*=5.4, 1H), 6.89 (t, *J*=9.3, 1H), 7.05 (bd, *J*=8.5, 1H), 7.18 (d, *J*=8.6, 2H), 7.43-7.48 (m, 3H), 8.27 (bs, 1H).

N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 88. Bromotrimethylsilane was added drop-wise to a stirring solution of **87** (475 mg, 0.630 mmol) in dry CH_2Cl_2 (5 mL). The resulting mixture was stirred for a further 16 hr then the solvent was removed under reduced pressure. The residue was resuspended in H_2O/MeOH and the slurry was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude product was purified by reverse phase HPLC (5:95 to 45:55, CH_3CN:H_2O, XTerra® Prep RP_{18}, 10 µm, 10x300 mm column) to give **88** as a colourless solid (73 mg, 17%). ^{1}H NMR (400 MHz, D_2O) δ 2.00 (s, 3H), 2.21 (tt, *J*=6.8, 21.7, 1H), 2.73 (t, J=6.5, 2H), 2.88 (t, J=6.5, 2H), 3.07-3.18 (m, 6H), 3.54-3.65 (m, 2H), 3.75-3.85 (m, 5H), 4.21 (t, *J*=9.1, 1H), 4.87-4.93 (m, 1H), 7.15-7.20 (m, 2H), 7.32-7.45 (m, 5H). ^{31}P NMR (162 MHz, D_2O): δ 20.40 (s, 2P); ^{19}F NMR (376 MHz, D_2O) δ -121.44 (dd, *J* = 15.3, 7.4); LCMS: 91.4% (254 nm), 89.9% (220 nm), weak (320 nm). MS: 698.1 (M-H).

Scheme 21. Synthesis of N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 90.

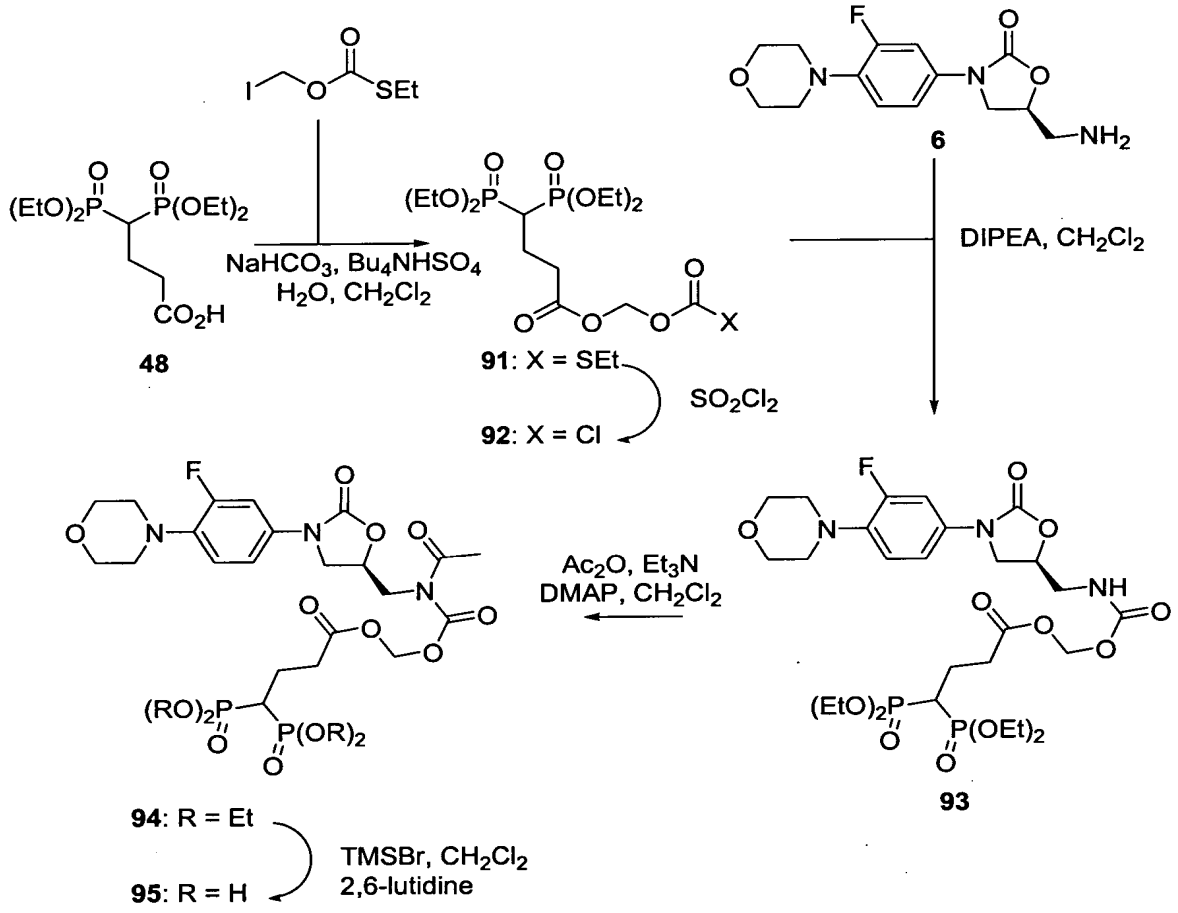


N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 89. Bisphosphonate alcohol **41** (152.5 mg, 0.4232 mmol) was added to the solution of carbonyldiimidazole (68.6 mg, 0.4231 mmol) in 2 mL of THF and another 1 mL of THF was used to rinse the alcohol. After 1h stirring at room temperature, the mixture was added to the suspension of compound **15** (142.6 mg, 0.4240 mmol), DBU (65 μL, 0.4259 mmol) and triethylamine (59 μL, 0.4227 mmol) in 2 mL of THF and another 1 mL of THF was used to rinse the first mixture. The reaction was stirred at room temperature overnight and then concentrated. Flash chromatography on silica gel with the elution of 8:1 (v/v) ethyl acetate/methanol to 6:1 to 5:1 afforded product **89** (190.9 mg, 62 %) as a slightly brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1, 12H), 1.64-1.70 (m, 4H), 1.88-2.04 (m, 2H), 2.02 (s, 3H), 2.28 (tt, *J* = 24.1, 6.1, 1H), 3.00 (bs, 2H), 3.56-3.77 (m, 7H), 4.02 (t, *J* = 9.0, 1H), 4.09-4.22 (m, 10H), 4.73-4.80 (m, 1H), 6.02 (t, *J* = 6.1, 1H), 6.92 (t, *J* = 9.2, 1H), 7.07 (dd, *J* = 9.4, 2.4, 1H), 7.45 (dd, *J* = 14.1, 2.5, 1H).

N-(((S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide bisphosphonate conjugate 90. Compound **89** (170 mg, 0.2352 mmol) in 3 mL of dichloromethane was treated with 0.6 mL (4.455 mmol) of TMSBr. After 2 days, the mixture was concentrated and the residue was taken up in small amount of water followed by the evaporation of the solvent. The process was repeated twice and at the end, the material in water gave a clear solution. This solution was carefully neutrallized to pH=7 with 0.5 M NaOH (aq) and evaporation of the solvent yielded a white solid. This material was applied to a Waters C18 Sep-Pak™ cartridge with water as the eluent. The fractions visible on TLC plates were combined and concentrated to afford the product **90** (110 mg, 77 %) as a white solid. ^{1}H NMR (400 MHz, D_2O) δ 1.56-1.88 (m, 7H), 1.99 (s, 3H), 3.06-3.08 (m, 4H), 3.54-3.74 (m, 6H), 3.83 (dd, *J* = 9.4, 6.1,

1H), 4.15 (t, J = 6.5, 2H), 4.21 (t, J = 9.2, 1H), 4.85-4.92 (m, 1H), 7.16-7.24 (m, 2H), 7.40-7.44 (m, 1H); ^{31}P NMR (162 MHz, D_2O) δ 21.28; ^{19}F NMR (376 MHz, D_2O) δ -121.41 (dd, J = 13.8, 8.6); MS: 609(M-H).

Scheme 21. Synthesis of Linezolid bisphosphonate conjugate 95.



O-(4,4-bis(diethylphosphono)butyryloxy)methyl S-ethyl carbonothioate (91). A mixture of **48** (1.01 g, 2.80 mmol), $NaHCO_3$ (471 mg, 5.61 mmol), and tetrabutylammonium hydrogensulfate (952 mg, 2.10 mmol) in CH_2Cl_2/H_2O (1:1, 50 mL) was stirred at room temperature for 50 minutes. A solution of *O*-iodomethyl *S*-ethyl carbonothioate (517 mg, 2.10 mmol) in CH_2Cl_2 (20 mL) was then added in 1 mL portions over approximately 40 minutes. The resulting mixture was stirred at room temperature for 16 hr. The organic phase was diluted with CH_2Cl_2 (50 mL) followed by washing with H_2O (50 mL), brine (50 mL) and drying over Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was resupended in EtO_2. After

filtering off the formed precipitate the filtrate was concentrated to give **91** (980 mg, 97%) as a pale yellow liquid that was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-1.38 (m, 15H), 2.19-2.30 (m, 2H), 2.49 (tt, *J*= 23.5, 6.7, 1H), 2.75 (t, *J*= 7.5, 2H), 2.89 (q, *J*= 7.3, 2H), 4.15-4.23 (m, 8H), 5.81 (s, 2H).

O-(4,4-Bis(diethylphosphono)butyryloxy)methyl chloroformate (92). A solution of **91** (491 mg, 1.03 mmol) and SO_2Cl_2 (125 uL, 1.54 mmol) in dry CH_2Cl_2 (5 mL) was stirred under argon at room temperature for 14 hr. The solvent was removed at reduced pressure to give **87** (358 mg, 77%) as a yellow liquid that was used with purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*= 7.0, 12H), 2.20-2.31 (m, 2H), 2.56 (tt, *J*= 23.7, 6.8, 1H), 2.72 (t, *J*= 7.3, 2H), 4.15-4.23 (m, 8H), 5.82 (s, 2H).

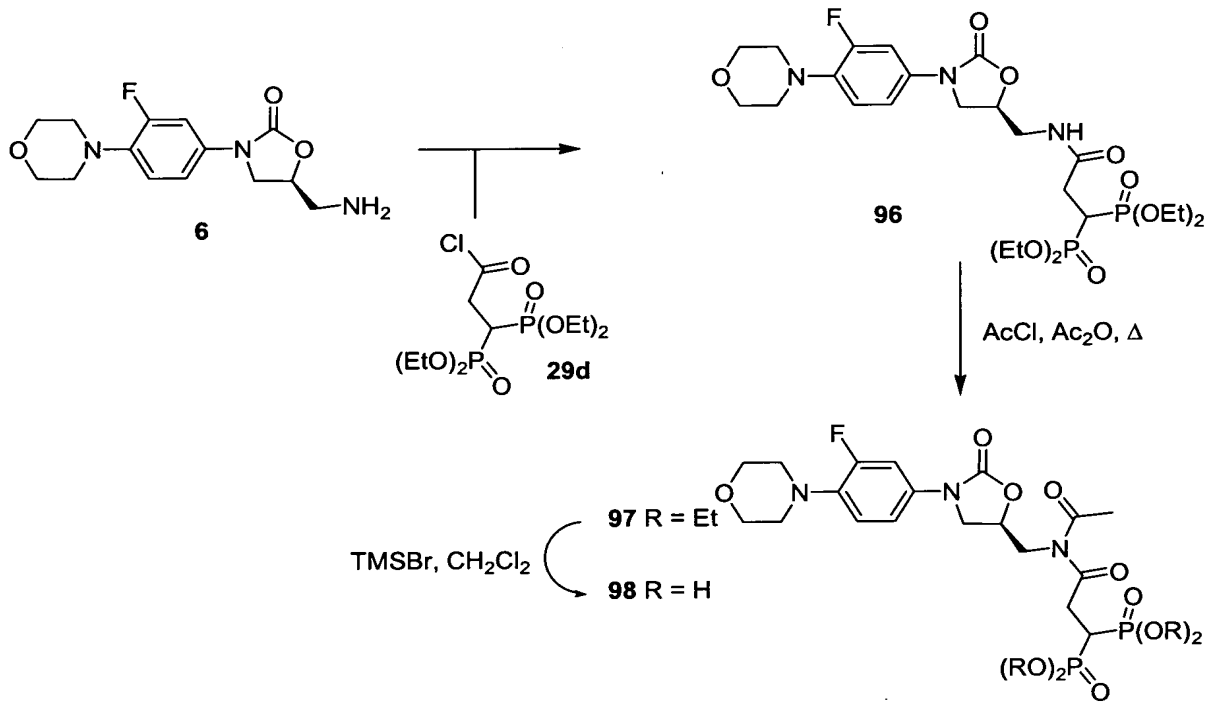
(4,4-Bis(diethylphosphono)butyryloxy)methyl ((S)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methylcarbamate (93). A solution of **6** (304 mg, 1.03 mmol) and diisopropylethylamine (357 uL, 2.03 mmol) in dry CH_2Cl_2 (7 mL) was cooled in an ice bath followed by the drop-wise addition of a solution of **92** (358 mg, 0.790 mmol) in dry CH_2Cl_2 (3 mL). The resulting mixture was alowed to warm to room temperature and stirring was continued for 18 hr at room temperature. The solution was diluted with CH_2Cl_2 (10 mL) followed by washing with 5% aqueous HCl (5 mL), 5% aqueous sodium bicarbonate (10 mL), H_2O (10 mL), saturated NaCl (10 mL) and drying over Na_2SO_4. The solvent was removed under reduced pressure resulting in the pale yellow coloured solid **93** (281 mg, 50%), which was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.36 (m, 12H), 2.16-2.31 (m, 2H), 2.39-2.56 (m, 1H), 2.71 (bt, *J*= 7.5, 2H), 3.12 (bt, *J*= 4.7, 4H), 3.52 (dt, *J*= 14.8, 6.1, 1H), 3.67 (ddd, *J*= 14.8, 6.7, 3.9, 1H), 3.76 (dd, *J*= 9.0, 6.9, 1H), 3.92 (bt, *J*= 4.7,4H), 4.05 (t, *J*= 8.8, 1H), 4.13-4.23 (m, 8H), 4.75-4.82 (m, 1H), 5.46 (bt, *J*= 6.2, 1H), 5.71 (d, *J*= 5.8, 1H), 5.75 (d, *J*= 5.8, 1H), 7.07-7.16 (m, 2H), 7.50 (d, *J*= 14.6, 1H).

(4,4-Bis(diethylphosphono)butyryloxy)methyl N-acetyl((S)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methylcarbamate (94). A solution of **93** (280 mg, .393 mmol), acetic anhydride (480 μL, 5.09 mmol), triethylamine (71 μL, 0.509 mmol) and dimethylaminopyridine (10 mg) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 14 hr. The reaction appeared to be approximately 30% complete by LCMS therefore, another portion of acetic anhydride (480 μL, 5.09 mmol) was added and the resulting solution was stirred for a further 18 hr. The solution was then diluted with CH_2Cl_2 (5 mL) and washed with cold 5% aqueous HCl, water and brine (10 mL each). The solvent was evaporated under reduced pressure and crude material was purified by silical gel chromatography on an automated flash

chromatography system(Biotage™) (0% to 5% MeOH in CH_2Cl_2) resulting in **94** (263 mg, 88%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J*= 6.8, 12H), 2.19-2.33 (m, 2H), 2.48 (tt, *J*=23.9, 6.4, 1H), 2.57 (s, 3H), 2.81 (t, *J*= 7.5, 2H), 3.12 (bs, 4H), 3.67 (t, *J*= 7.6, 1H), 3.92 (bs, 4H), 4.00-4.10 (m, 3H), 4.13-4.22 (m, 8H), 4.77-4.84 (m, 1H), 5.85 (d, *J*= 5.8, 1H), 5.88 (d, *J*= 5.8, 1H), 7.07-7.13 (m, 2H), 7.49 (d, *J*= 14.3, 1H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.9 (s, 2P).

(4,4-Bisphosphonobutyryloxy)methyl acetyl((R)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methylcarbamate (95). Bromotrimethylsilane (683 μL, 5.17 mmol) was added drop-wise to a stirring solution of **94** (260 mg, 0.345 mmol) and 2,6-lutidine (801 μL, 6.90 mmol) in dry CH_2Cl_2 (5 mL) which was cooled in an ice-bath. The resulting mixture was stirred while warming to room temperature over 20 hr. The solution was again cooled in an ice-bath followed by the addition of MeOH (2 mL). After stirring the solution for 10 min the solvent was removed under reduced pressure. The crude product was purified by WATERS C18 silica chromatogaphy on an automated flash chromatography system (Biotage™) (0% to 50% CH_3CN in H_2O) resulting in the mono-2,6-lutidine salt of **95** as a colourless solid (205 mg, 79%). ^{1}H NMR (400 MHz, D_2O) δ 2.02-2.19 (m, 3H), 2.52 (s, 3H), 2.77 (t, *J*= 7.4, 2H), 3.21 (bt, *J*= 4.5, 4H), 3.83 (dd, *J*= 9.7, 5.0, 1H), 3.94 (bt, *J*= 4.5, 4H), 4.02 (dd, *J*= 15.0, 4.2, 1H), 4.20-4.29 (m, 2H), 4.92-4.98 (m, 1H), 5.87 (s, 2H), 7.22-7.31 (m, 2H), 7.44 (dd, *J*= 13.9, 2.4, 1H); ^{31}P NMR (162 MHz, D_2O) δ 21.00 (bs, 2P); ^{19}F NMR (376 MHz, D_2O) δ 21.00 (dd, *J*= 13.7, 9.1, 1F); MS: 642.2 (M+H).

Scheme 22. Synthesis of Linezolid bisphosphonate conjugate 98.



N-(((S)-3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)-3,3-bis(diethylphosphono)propionamide (96). To a stirred solution of amine **6** (0.511 g, 1.73 mmol) in anhydrous CH_2Cl_2 (10 mL) held at 0 °C were added sequentially Hunig's base (0.603 mL, 3.46 mmol) and a solution of **29d** (1.73 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was then allowed to warm to room temperature with stirring overnight. It was then diluted with further CH_2Cl_2, washed with water, the aqueous re-extracted with CH_2Cl_2, and the combined organics washed twice with 1M HCl and once with brine. After drying over $MgSO_4$ and evaporation the product was obtained essentially pure (0.60 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.38 (m, 12H), 2.76 (td, *J*=16.5, 6.2, 2H), 3.03-3.08 (m, 4H), 3.15 (tt, *J*=23.7, 6.1, 1H), 3.57-3.74 (m, 2H), 3.79-3.84 (m, 1H), 3.85-3.90 (m, 4H), 3.98 (t, *J*=8.8, 1H), 4.07-4.23 (m, 8H), 4.70-4.82 (m, 1H), 6.83-6.92 (m, 1H), 6.95 (t, *J*=9.0, 1H), 7.11 (dd, *J*=8.8, 1.5, 1H), 7.44 (dd, *J*=14.3, 2.6, 1H).

N-Acetyl-N-(((S)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)-3,3-bis(diethylphosphono)propionamide (97). A stirred solution of amide **96** (0.2018 g, 0.324 mmol) and acetyl chloride (0.6 mL, 8.4 mmol) in acetic anhydride (4 mL) was heated at reflux for 3 h. The solvent was evaporated, and the residue dissolved in ethyl acetate (50 mL) and washed with ice-cold saturated aqueous $NaHCO_3$ (2x 50 mL), brine (50 mL), dried ($MgSO_4$), and evaporated to give essentially pure **97** (0.1953 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.38 (m, 12H), 2.48 (s, 3H), 3.04-3.11 (m, 4H), 3.27-3.47 (m, 3H), 3.75 (dd, *J*=9.3, 7.1, 1H), 3.86-3.96

(m, 5H), 4.09 (t, *J*=9.0, 1H), 4.13-4.26 (m, 9H), 4.82-4.91 (m, 1H), 6.93-7.30 (m, 1H), 7.08-7.13 (m, 1H), 7.45 (dd, *J*=14.3, 2.6, 1H).

N-Acetyl-N-(((S)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)-3,3-bisphosphonopropionamide (98). TMSBr (0.58 mL, 4.4 mmol) was added in one portion to a stirring solution of **97** (195.3 mg, 0.293 mmol) and 2,6-lutidine (0.68 mL, 5.86 mmol) in anhydrous CH_2Cl_2 (10 mL) and the resulting mixture was stirred 24 h at room temperature. The solvent was evaporated and the residue treated with ice-water (20 mL), rapidly bringing to pH 7 with 1M NaOH. This mixture was evaporated, and the residue subjected to purification by Waters C18 sep-pak™ (twice) eluting with water to give **98** as a colourless solid (0.048 g, 27% based on product being disodium salt). ^{1}H NMR (400 MHz, D_2O) δ 2.47 (s, 3H), 2.79 (tt, *J*=21.8, 6.4, 1H), 3.10-3.16 (m, 4H), 3.17-3.28 (m, 2H), 3.90-3.96 (m, 5H), 4.15-4.31 (m, 3H), 5.02-5.10 (m, 1H), 7.19-7.27 (m, 2H), 7.41-7.47 (m, 1H).

Example 2: Binding of bisphosphonated derivatives of oxazolidinones to hydroxyapatite powder

An *in vitro* experiment was conducted for testing the bone-affinity of some of the phosphonated derivatives of oxazolidinones synthesized. Hydroxyapatite powder was selected for mimicking bone texture as it is the principal mineral component forming bone tissues. Eperezolid was used as a negative control and tetracycline (an antibiotic recognized as having a binding affinity for bones) was used as a positive control.

Briefly, a stock solution (5 x 10^{-3}M) of each of the compounds to be tested was added to 0.1M Tris-HCl buffer pH 7, 0.15M NaCl to get a final concentration of 10^{-4}M. Triplicate samples (1 mL) of the compound solutions were intensively shaken for 10 min with or without 10 µL of a hydroxyapatite (HDA) suspension (Sigma H-0252). The samples were then centrifuged for 15 min at 10,000 g. The presence of unbond compound was measured by injection of 30 µL of each of the supernatants into an Agilent 1100™ LC/UV system. Results are presented in **Figure 1** as mean of triplicate measurement ±SD. Percentage of compound not bond to the hydroxyapatite was evaluated as: (peak area with HDA / peak area without HDA) X 100%.

As shown in **Figure 1**, both phosphonated derivatives of oxazolidinones tested (compounds **60** and **62**) bond entirely (100% binding) to the hydroxyapatite powder during the 10 min incubation. In contrast, less than 1.5% of eperezolid bond to the hydroxyapatite powder during the same period of time. These results clearly demonstrate a dramatically increased

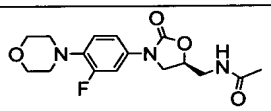
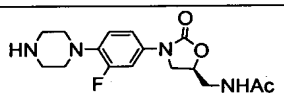
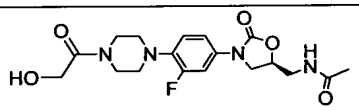
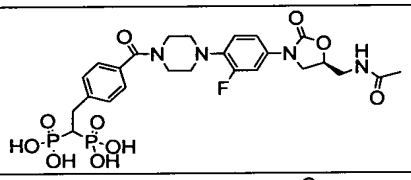
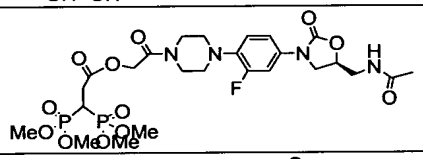
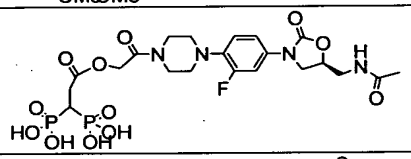
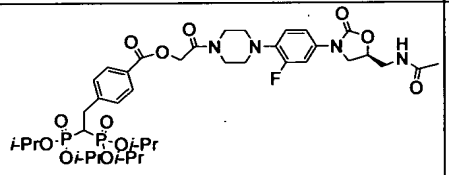
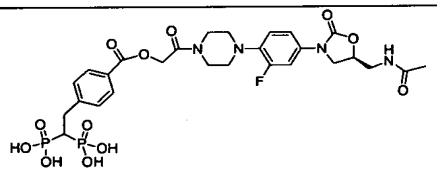
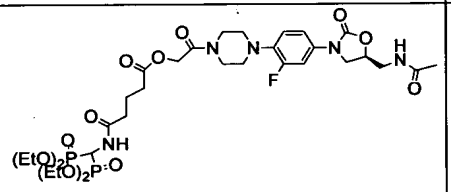
binding affinity of the synthesized phosphonated derivatives of oxazolidinones for osseous materials. In additon, and more significantly, later results convincingly demonstrated the binding of **72** and **74** to bone *in vivo* (see **Examples 6** and **7** below).

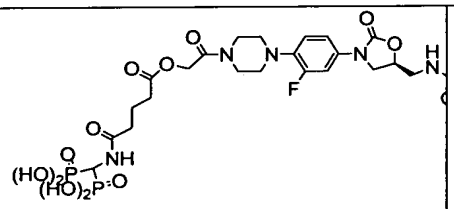
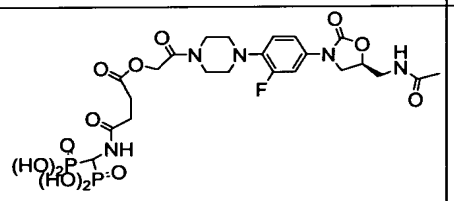
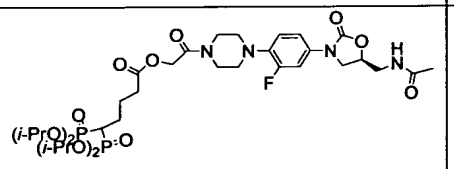
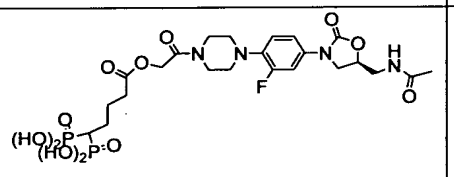
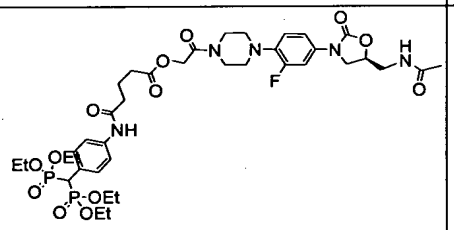
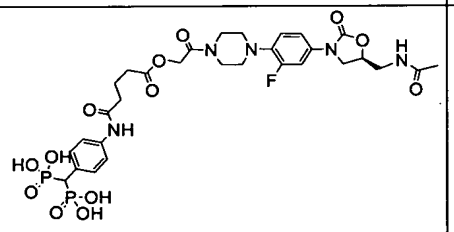
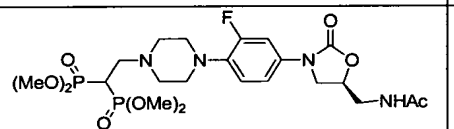
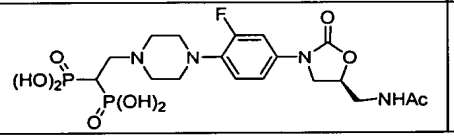
Example 3: MIC determination of linezolid and eperezolid bisphosphonate conjugates

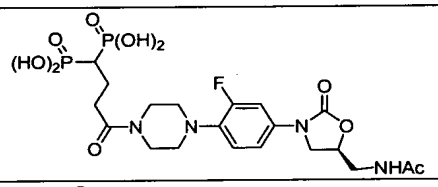
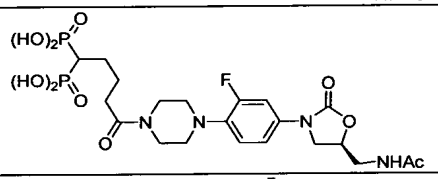
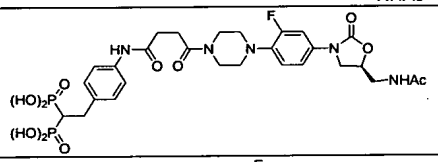
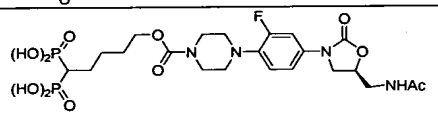
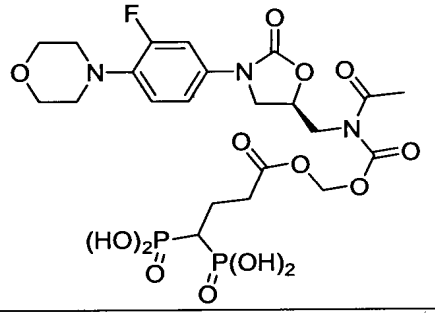
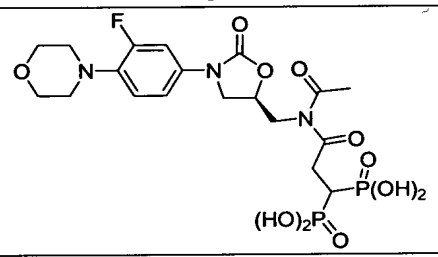
Susceptibility of *S. aureus* strains RN4220 and ATCC13709 to commercial antibiotics (data not shown) and synthesized compounds was determined by following the guidelines set by the Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards, NCCLS) (M26-A). Compounds were diluted two-fold serially in DMSO and transferred to cation-adjusted Mueller Hinton broth (CAMHB; Becton Dickinson). 50 µL of compounds diluted in CAMHB was mixed with 100 µL of bacteria diluted in CAMHB in 96-well microtiter plates. The final number of micro-organisms in the assay was $5x10^5$ c.f.u. per mL and the final concentration of DMSO in the assay was 1.25%. Assays were set up in duplicate and incubated at 37 °C for 18 h. The concentration of compound that inhibited visible growth was reported as the minimum inhibitory concentration (MIC).

Susceptibility testing experiments were also carried out in the presence of serum. These experiments were carried out similar to the susceptibility testing above with the following modifications. 75 µL of compounds diluted in CAMHB was mixed with 75 µL of bacteria diluted in 100% serum from any given source (commercial pooled mouse serum (MS) and human serum (HS), Equitech-Bio Inc.) or diluted in 8% purified human serum albumin (HSA) (Calbiochem). The final concentration of animal serum in the assay was 50% and the final concentration of purified human serum albumin in the assay was 4%; the concentrations of all other components were identical to those described for susceptibility testing. The results are reported in **Table 1.**

TABLE 1: MIC determination of selected linezolid and eperezolid bisphosphonate conjugates

No.	Structure	MIC vs. S. aureus (μg/ml)							
		RN4220				ATCC13709			
		CA MHB	50% MS	50% HS	4% HSA	CA MHB	50% MS	50% HS	4% HSA
7		0.5	0.5	1	1	4	2	4	4
15		4-8	2	16	8	4	1	8	4
17		1	0.5	1	0.5	1	1	2	1
66		32	> 128	128	> 128	64	128	> 128	> 128
67		32	1	16	8-16	32	2	16-32	16-32
68		2	n.d.	n.d.	n.d.	4	4	4	8
69		64	2	64-128	128	> 128	4-8	128	> 128
70		27.6	n.d.	n.d.	n.d.	27.6	27.6	27.6	27.6
71		32	n.d.	n.d.	n.d.	64	2	64	64

72		2	n.d.	n.d.	n.d.	4	32	32	64
74		8	n.d.	n.d.	n.d.	8	8	8	32
75		64-128	n.d.	n.d.	n.d.	> 128	2	64	128
76		32-64	n.d.	n.d.	n.d.	128	64	64	64
77		64	n.d.	n.d.	n.d.	32	4	16	n.d.
78		16	n.d.	n.d.	n.d.	64	16	64	>64
79		8				8	2	16	8
80		>64	n.d.	n.d.	n.d.	>64	>64	>64	>64

82		> 128	n.d.	n.d.	n.d.	> 128	> 128	> 128	> 128
84		> 128	n.d.	n.d.	n.d.	> 128	> 128	> 128	> 128
88		128	n.d.	n.d.	n.d.	> 128	> 128	> 128	> 128
90		> 128	n.d.	n.d.	n.d.	> 128	> 128	> 128	> 128
95		4	n.d.	n.d.	n.d.	4	4	8	n.d.
98		4	n.d.	n.d.	n.d.	4	4	4	n.d.

CAMHB: cation adjusted Mueller-Hinton broth. 50%MS: 50% Mouse serum in cation adjusted Mueller-Hinton broth. 50%HS: 50% Human serum in cation adjusted Mueller-Hinton broth. 4% HSA: 4% Human serum albumin in cation adjusted Mueller-Hinton broth. n.d.: Not determined.

As shown in **Table 1**, several of the phosphonated oxazolidinone derivatives tested exhibited antibacterial activity in CAMHB. Interestingly, the bisphosphonated ester derivatives of eperezolid **67**, **69**, **71**, **75** and **77** all showed significantly increased antibacterial activity in the presence of mouse serum, suggesting that these compounds were good substrates for esterases present in high concentrations in mouse blood, and that eperezolid was rapidly released. This also suggests that the antibacterial activity proper to the free bisphosphonated prodrugs is insignificant, and that a cleavage step is generally required to result in bacterial

killing. This mode of cleavage was further studied below (see **Example 4**). Esterase activity seems to be much lower with the deprotected bisphosphonic acids versus the equivalent protected derivatives. Hence, compounds **69** and **75** have much lower MIC values in mouse serum, while the presence of mouse serum does not affect the MIC values of **76**. The impact of serum on the MIC values of compound **72**, **74**, **95** and **98** is marginal, and these values are fairly low for **74**, **95** and **98**. This suggests that for these compounds there is an ability to regenerate the parent drug by chemically induced decomposition, and that enzymatic cleavage is not required. Thus the MIC of **74** is relatively low and independent of the medium, whereas a large decrease in MIC for its precursor **73** is observed in the presence of mouse serum. The cleavage of compounds **72** and **74** is also thought to be assisted by an intramolecular mechanism involving the nitrogen atom of the linker, accounting for their similar MIC values in different media.

Cytotoxicity assays

Selected compounds were also tested for their ability to inhibit growth of mammalian cells so as to ascertain levels of cytotoxicity to the mammalian host. Two assays were used: ATP and MTS assays. Assays were performed in 96-well microtiter plates. In the ATP assay the production of ATP was used as the indicator of cell viability and in the MTS assay the production of reducing equivalents was used as the indicator of cell viability. Cryopreserved primary human hepatocytes (In vitro technologies) were used in the ATP assay and cultured Hela cells (Promega) were used in the MTS assay. For the ATP assay, compounds at 100, 50, 25, and 12.5 μM were incubated with $1x10^4$ primary human hepatocytes per well in Krebs-Henseleit Buffer (Sigma) for two hours at 37 °C under 5% CO_2. At the end of the incubation, the ATP content was determined by the addition of luciferin and luciferase and measurement of luminescence. For the MTS assay, compounds at 100, 50, 25, and 12.5 μM were incubated with $2x10^4$ Hela cells per well in Dulbecco's Modified Eagle Medium (Invitrogen Corporation) containing 1% Bovine Growth Serum (HyClone) for 18 h at 37 °C under 5% CO_2. At the end of the incubation, the amount of reducing equivalents was determined by the reduction of MTS reagent (3-(4,5-dimethylthiazol-2-yl)-5-(3 carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium inner salt) to formazan product ((4,5-dimethylthiazol-2-yl)-3-(3-carboxymethoxyphenyl)-5-(4-sulfophenyl)-formazan) as revealed by absorbance at 490 nm.

Compounds **67**, **68**, **69**, **71**, **72**, **74**, **75**, **76**, **77**, **78**, **80**, **82**, **84**, **88** and **90** were all tested in the MTS assay. Compounds **72** and **74** were also tested in the ATP assay. No significant

toxicity was observed for any of the compounds tested, even at the highest doses (data not shown).

Example 4: Cleavage of linkers by esterase-like activity in serum

To demonstrate directly that **67** and **69** were processed to release eperezolid by esterases present in serum (see previous Example), the fate of these two compounds in the presence of serum was evaluated by LC/MS. Briefly, MIC assays were set up in the presence of serum as described previously. Rat serum was purchased from Equitech-Bio Inc. and fresh human serum was obtained from four volunteers. To the well corresponding to the MIC for that compound, an equal volume of HPLC-grade methanol was added. After vortexing and centrifugation, the methanol-extracted material was subjected to evaluation by LC/MS. The results are reported in **Table 2** as percentage of original compound detected after 24 h incubation in serum as compared to original amount loaded.

Table 2: LC/MS analysis showing cleavage of linkers in serum

Serum source	Percentage of total compounds detected			
	67	Eperezolid	69	Eperezolid
Mouse	0	100	0	100
Rat	62	38	18	82
Human (commercial)	99.2	0.8	99.7	0.3
Human (fresh)	87	13	96	4

As shown in **Table 2**, rat and particularly mouse serum were very efficient in generating eperezolid from the prodrugs **67** and **69**. However, the human serum was only slightly effective in the conversion of prodrug to drug. This suggests, not unexpectedly, that esterases with specificity for these compounds are more abundant in rodents than in humans. Fresh human serum also appeared significantly more effective than commercially available pooled human serum. As was noted previously (see **Table 1**), the deprotected bisphosphonic acids such as **68** and **70** MIC values are not affected by the presence of either mouse serum or human serum.

This LC/MS analysis correlates the lower MIC values of prodrugs **67** and **69** in mouse serum with the far greater rate of cleavage in this medium. This adds weight to the argument that the antibacterial activity associated with the bisphosphonate prodrugs is likely due to cleavage to the parent drug.

Example 5: ***in vitro*** **coupled transcription-translation assay**

A kit for the *E. coli* S30 extract system for circular DNA from Promega™ was used to assess the effect of the synthesized compounds on *in vitro* coupled transcription-translation, which is known to be inhibited by the oxazolidinone class of antibacterials. The procedure was as described by the manufacturer for reactions using ^{35}S-Methionine except that DMSO (2% final concentration) was included in each reaction. Compounds were added at 20 µM per reaction. After 90 min incubation at 30°C , the mixture was added to a Luciferase Assay Reagent (Promega™) and the luminescence generated was measured.

Inhibition of RNA transcription and/or protein translation in the *in vitro* transcription translation assay results in the lack of detection of the luciferase activity. **Figure 2** shows that, as expected eperezolid, known to inhibit translation, efficiently prevented the production of luciferase. Controls for inhibition of translation and transcription (erythromycin and rifampicin, respectively, results not shown) also inhibited the synthesis of luciferase, while ciprofloxacin (a DNA synthesis inhibitor) did not affect luciferase synthesis. The MIC assays (**Table 1**) suggested compounds **68**, **70** and **72**, deprotected bisphosphonic acid derivatives of eperezolid with noticeable antibacterial activity, to release eperezolid under the test conditions. On the other hand, in the absence of serum, **67**, **69** and **71**, their respective parent bisphosphonate esters (protected prodrugs) produced high MIC values and thus failed to regenerate eperezolid under the same conditions. This is perfectly consistent with the data produced by this assay, whereby **68**, **70** and **72** starkly reduced the production of Luciferase, whereas **67**, **69** and **71** were unable to do. Not surprisingly, the deprotected bisphosphonate prodrug **80** was inactive in the MIC assay –suggesting it not to cleave to Eperezolid- and was also poorly inhibitory in the transcription/translation assay. Its parent compound **79** displayed activity in both assay, suggesting it to either cleave to Eperezolid or to have antibacterial and inhibitory activity of its own. The correlation between the MIC assay and this assay additionally supports the notion that the mode of action of these prodrugs is the same as that of the parent oxazolidinones.

Example 6: LC/MS analysis of samples from mice treated with bisphosphonated eperezolid prodrugs

In order to investigate the binding of bisphosphonated eperezolid prodrugs to bone *in vivo*, mice were treated with eperezolid amine **15**, eperezolid **17**, and bisphosphonated eperezolid conjugates **68**, **72**, **74**, and **80** and the drug content of the mouse femurs was analyzed at 1 h and at 24 h after injection. Each mouse was administered a single bolus intravenous (tail vein) dose of one of the compounds dissolved in 0.85% NaCl at 10 mg/kg of body weight. Groups of three mice were used for each experimental time point. Animals were humanely sacrificed at 1 and 24 h after i.v. dosing to evaluate the binding (if any) of the compounds to the bone. Femurs were recovered by dissection, cleaned from soft tissues and kept at -80 °C before determination of the drug concentration of the bone.

Extraction procedure

An extraction procedure was devised whereby the bone was dissolved in acid, then basified and extracted with methanol. Under these conditions all of the compounds were cleaved to eperezolid amine **15**. Hence in each case the effectiveness of each of the compounds in binding to bone was measured by determining the concentration of **15** in the bone sample following extraction.

The dried mouse femur was weighed, added to 400 µL 6M HCl and incubated at 50 °C for 2 h. At the end of this period 200 µL 10M NaOH and 400 µL methanol were added to each sample. The samples were vortexed 15 min and centrifuged 10 min at 10,000 g. The supernatant was transferred into another vial and centrifuged again in the same conditions. 20 µL of the last supernatant was injected into the LC/MS. Unknown samples were evaluated against a calibration curve of eperezolid amine (10 to 1000 ng/mL) from standards prepared in spiked blank femur and treated in the same manner as the unknowns.

LC/MS analysis

The samples were injected on a Zorbax™ SB-AQ (3.5 µ, 2.1 x 30 mm) column with a flow rate of 0.3 mL/min using ammonium acetate 10mM pH 6.8 (aq) and acetonitrile (org) as eluents with the following program: 0-3 min: 12 → 20% org; 3-6 min: 20 → 50% org; 6-9 min: 50 → 80% org; 9-10min: 80 → 12% org; 10-15min: 12% org.

The APCI/ESI source was used on the MS trap (Agilent SL) in positive polarity with dry temperature set at 350 °C, dry gas set at 10 L/min and nebulizer set at 45 psi. The acquisition spectrum was divided into 2 segments: the divert valve was selected in the first segment (0-2

min), followed by an SRM on MH^+ 337.1 (eperezolid amine) and 395.2 (eperezolid) for segment 2 (2-15min).

As shown in **Figure 3**, when either eperezolid amine or eperezolid was directly injected into the mouse, the level of each compound found in mouse femur was very low after 1h, and inexistent after 24h. This result is fully consistent with the *in vitro* experiment of Example 2, where it was found that the affinity of eperezolid for the major bone component hydoxyapatite was very low indeed. All of the bisphosphonated compounds **68**, **72**, **74**, and **80**, in which eperezolid or eperezolid amine is coupled to a bisphosphonate, the compounds are rapidly concentrated in bone. Compound **68** is more poorly concentrated in the bone, suggesting it to possibly hydrolyze in serum prior to attachment. For compounds **72**, **74** and **80**, however, the linkers are clearly not cleaved to any great extent before the bisphosphonic acid of the molecule is able to bind to the bones, and the previously observed *in vitro* high affinity of this group for hydoxyapatite is reproduced *in vivo*. After 24h, it is clear that the level of compounds **72** and **74** has somewhat decreased, suggesting a slow liberation of eperezolid. Compound **80**, which both the MIC assay and the Transcription/Translation assays suggested not to be able to release the parent drug, expectedly remains essentially at the same level in bone. This experiment suggests compounds **72** and **74** to be able to concentrate in bone and slowly release eperezolid over time.

Example 7: LC/MS analysis of samples from rat treated with compounds 72

Having established the remarkable efficacy of the bisphosphonic acid groups of compounds **72** and **74** in binding to bone *in vivo*, the potential for *in vivo* cleavage of these two compounds to eperezolid with prodrug **72** was further investigated, in particular to determine the half-life of this process. Rats were given doses of **72** differing by a factor of ten to study what effect this would have on the subsequent blood- and bone-concentrations of the both prodrug and drug. In further experiments, rats were given the higher (10 mg/kg) dose, and the kinetics for the generation of eperezolid in bone were determined.

Administration of Compounds

Rats were administered a single bolus intravenous (tail vein) dose of **72** dissolved in 0.85% NaCl at 1 or 10 mg/kg of body weight. Groups of three rats were used for each experimental time point. Animals were humanely sacrificed at 1 and 24 h after i.v. dosing to evaluate the binding of the drug to the bone, and at 1 h, 24 h, 7 days, 14 days and 28 days after i.v. dosing to determine the half-life of **72** in bone. Blood samples (one from each animal) were

collected by cardiac puncture. Plasma was separated from whole blood and kept at -80 °C prior to analysis. Tibia were recovered by dissection, cleaned from soft tissues and kept at -80 °C prior to concentration determination of the compound.

Bone Extraction procedure

The dried rat tibia was powdered and two fractions of 100 mg were weighed.

For the dosage of regenerated eperezolid **17,** that is eperezolid **17** resulting from the hydrolysis of the prodrug (compound **72**), to one fraction of bone powder was added 1.8 mL phosphate buffer 100mM pH 7.5 and incubated at room temperature for 2 h. After the addition of an internal standard, the samples were centrifuged 10 min at 10,000 g and extracted by solid phase extraction on Strata™ (60 mg/3 mL) cartridge. The eluent (methanol) was evaporated to dryness, the dried residue reconstituted into 200 µL water and 20 µL injected into the LC/MS. Unknown samples were evaluated against a calibration curve of eperezolid (10 to 1000 ng/mL) from standards prepared in spiked blank bone powder and treated as the unknowns.

The total dosage of the prodrug (**72**) plus regenerated eperezolid (**17**) was made by analysis of the isolated eperezolid amine **15**. The second fraction of tibia was incubated in 800 µL 6M HCl at 50 °C for 5 h. In those conditions **72** and **17** were cleaved into eperezolid amine **15**. 10M NaOH (400 µL), internal standard and water (600 µL) were added to the samples at the end of the incubation period, the mixture vortexed and centrifuged for 10 min at 10,000 g. The supernatant was extracted on Strata™ cartridge (60 mg/3 mL). The eluent (methanol) was evaporated to dryness, the dried residue reconstituted into 200 µL water and 20 µL injected into the LC/MS. Unknown samples were evaluated against a calibration curve of eperezolid amine (50 to 5000 ng/mL) from standards prepared in blank bone powder and treated as the unknowns.

The rat plasma was also analysed as two identical fractions (100 µL each).

For the dosage of the regenerated eperezolid, to one fraction of plasma was added 900 µL water and an internal standard. The sample was extracted on Strata™ (30 mg/1 mL) cartridge. The eluent (methanol) was evaporated to dryness, the dried residue reconstituted into 100 µL water and 20 µL injected into the LC/MS. The unknown samples were evaluated against a calibration curve (10 to 2000 ng/mL) of eperezolid from standards prepared in spiked blank plasma and treated as the unknowns.

For the dosage of the total prodrug and regenerated drug, the second fraction of plasma was incubated at 50 °C for 2 h with 200 µL of 6M HCl. At the end of this period, water (600 µL) and internal standard were added, the mixture vortexed and centrifuged (10 min, 10,000 g). The

supernatant was extracted on Strata™ (30 mg/1 mL) cartridge. The eluent (methanol) was evaporated to dryness, the dried residue reconstituted into 100 µL water and 20 µL injected into the LC/MS. The unknown samples were evaluated against a calibration curve (50 to 10,000 ng/mL) of eperezolid amine from standards prepared in spiked blank plasma and treated as the unknowns.

LC/MS analysis

The samples were injected on a Zorbax™ SB-AQ (3.5µ, 2.1 x 30 mm) column with a flow rate of 0.3 mL/min using ammonium acetate 10mM pH 6.8 (aq) and acetonitrile (org) as eluents with the following program: 0-3 min: 12 → 20% org; 3-6 min: 20 → 50% org; 6-9 min: 50 → 80% org; 9-10min: 80 → 12% org; 10-15min: 12% org. The APCI/ESI source was used on the MS trap (Agilent SL) in positive polarity with dry temperature set at 350 °C, dry gas set at 10 L/min and nebulizer sets at 45 psi. The acquisition spectrum was divided into 3 segments: the divert valve was selected in the first segment (0-2min), followed by an SRM on MH^+ 337.1 (eperezolid amine) and 395.2 (eperezolid) for segment 2 (2-6.8min) and by SRM on MH^+ 338.2 (internal standard) for segment 3 (6.8-15min).

*Level of total eperezolid amine (compound **72** plus eperezolid) found in plasma and tibia of rat following an IV bolus at 1 and 10 mg/kg*

As shown at **Figure 4**, it was found that a ten-fold increase in the dose of **72** led to a ten-fold increase in the amount of total eperezolid amine **15** found in plasma after 1 h. The level of **15** at 24 h was too low to be evaluated, suggesting that all prodrug **72** has been cleared from plasma after 24h, presumably by uptake into bone, excretion or metabolic clearance. The level of regenerated eperezolid **17** (eperezolid resulting from prodrug cleavage under physiological conditions) was too low to be evaluated at 1 h and at 24 h. Further, **72** is sufficiently stable in rat blood that its degree of cleavage to **17** in one hour is negligible. These results emphasize the potential of prodrugs such as **72** with low cleavage in serum and rapid concentration in bone.

As shown in **Figures 5A** and **5B**, increasing the dose of **72** injected from 1 mg/kg to 10 mg/kg led to an increase in the level of total eperezolid amine **15** in the tibia of roughly five times. The amount of regenerated eperezolid **17** (eperezolid resulting from prodrug cleavage under physiological conditions) was increased by a similar amount. Thus, there is a correlation between the dose and the concentration of both drug and prodrug in bone. The lower efficiency of accumulation in bone at 10mg/kg may be attributable to a number of physiological processes,

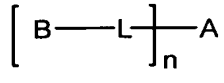
in particular clearance of precipitated prodrug particulates which would be more prevalent at higher concentration.

The kinetics of the disappearance of **72** and the generation of Eperezolid **17** are shown in **Figure 6.** The half-life of **72** in bone was determined to be 6.1 days. It is remarkable that a close to steady state concentration of **17** in bone is achieved from a single relatively low dose of **72**, and that a detectable amount of eperezolid persists in the bone after a period of at least 28 days. This pharmacokinetic profile may be expected to be highly advantageous for treatment of chronic osteomyelitis, where the risk of relapse from current treatment regimens is very high, or in the prevention of osteomyelitis, where a small concentration of drug present at all times would prevent bacterial growth.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound represented by the general Formula (I):



(I)

as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

A is an oxazolidinone antimicrobial molecule;

B is a phosphonated group having a high affinity to osseous tissues;

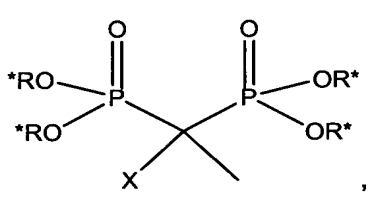
L is a bond or a linker for covalently coupling B to A; and

n is an 1,2 or 3.

2. The compound of claim 1, wherein n is 1.

3. The compound of claim 1, wherein B is a bisphosphonate.

4. The compound of claim 3, wherein said bisphosphonate is selected from the group consisting of:



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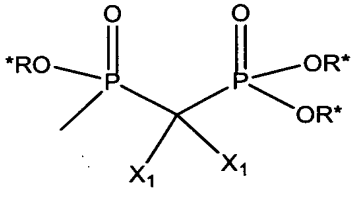

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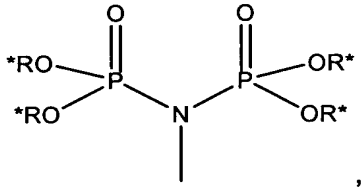


,

wherein:

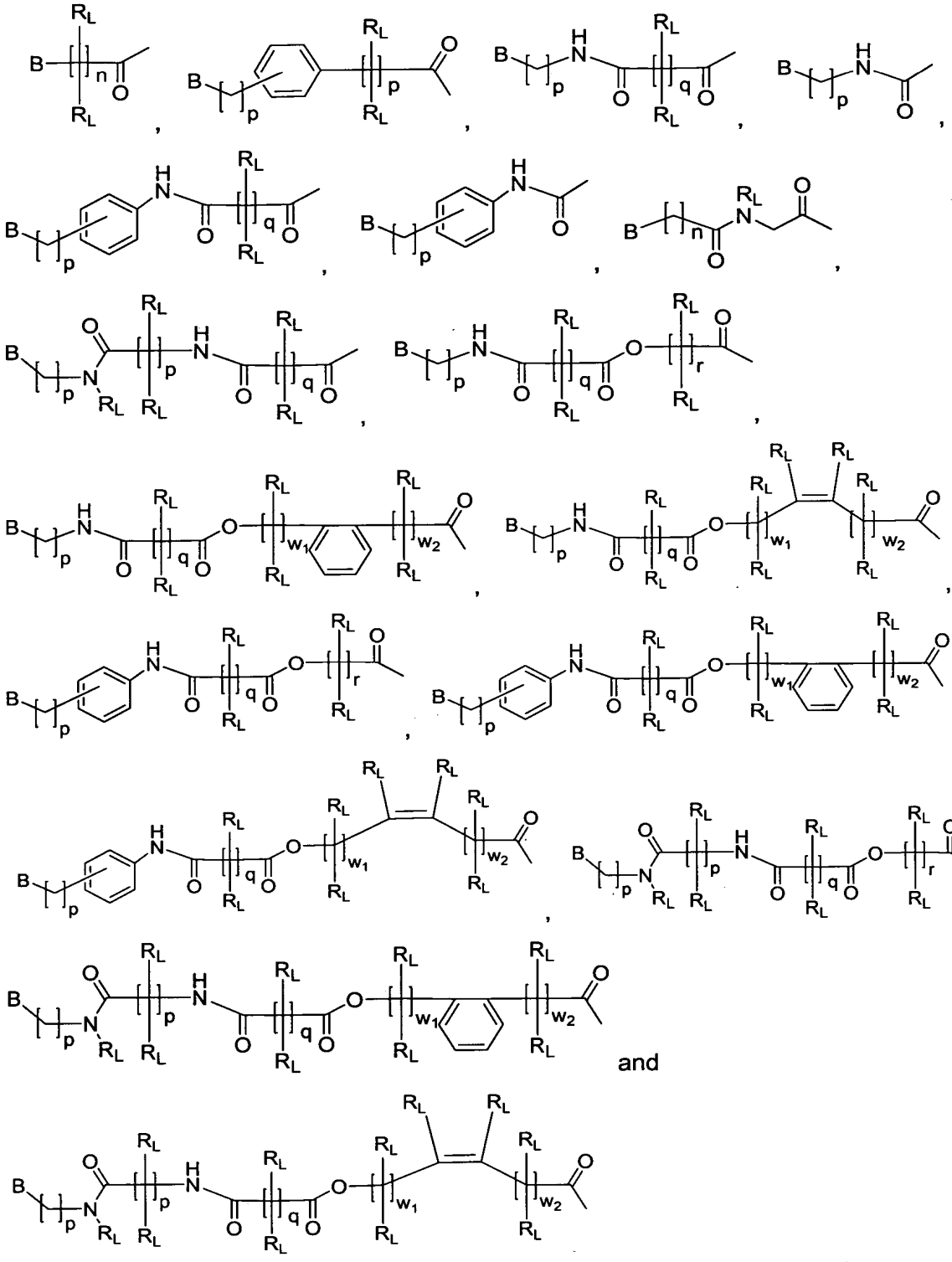
each **R*** is independently selected from the group consisting of H, lower alkyl, cycloalkyl, aryl and heteroaryl, with the proviso that at least two **R*** are H;

X is H, OH, NH_2, or a halo group; and

$\mathbf{X_1}$ are both H, or each is independently selected from the group consisting of H, OH, NH_2, and a halo group.

5. The compound of claim 1, wherein L is a hydrolysable linker.

6. The compound of claim 1, wherein at least one of said **B—L—** is coupled to a hydroxyl functionality on said oxazolidinone **A**, and wherein each of said **B—L—** coupled to a hydroxyl functionality is independently selected from the group consisting of:



and

wherein:

B represents said phosphonated group;

each **p** is independently 0 or an integer ≤ 10;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl;

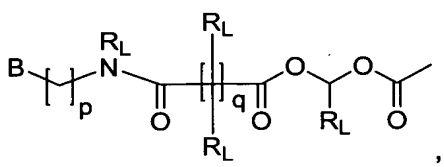
q is 2 or 3;

n is an integer ≤ 10;

r is 1, 2, 3, 4 or 5; and

$\mathbf{w_1}$ and $\mathbf{w_2}$ are each integers ≥ 0 such that their sum ($\mathbf{w_1} + \mathbf{w_2}$) is 1, 2 or 3.

7. The compound of claim 1, wherein at least one of said **B—L—** is coupled to a nitrogen atom on said oxazolidinone **A**, and wherein each of said **B—L—** coupled to a nitrogen atom is independently selected from the group consisting of: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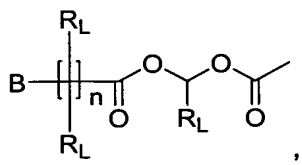
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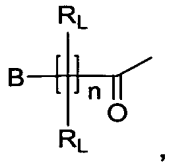
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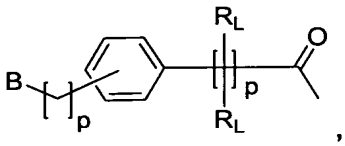
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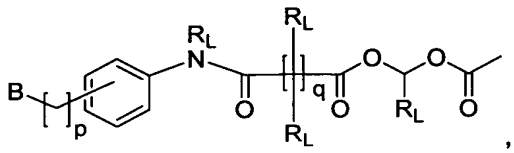
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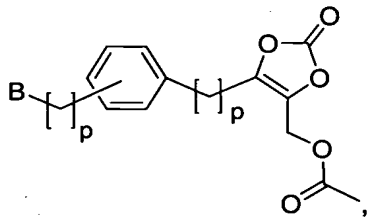
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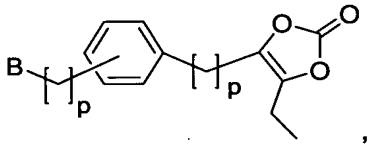
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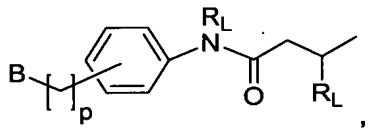
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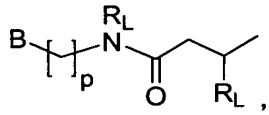
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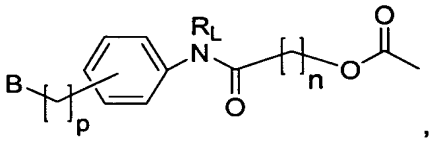
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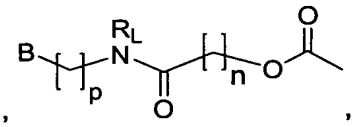
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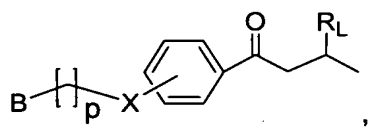
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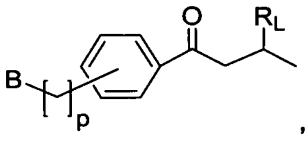
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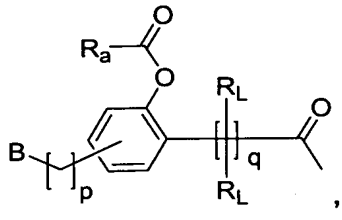
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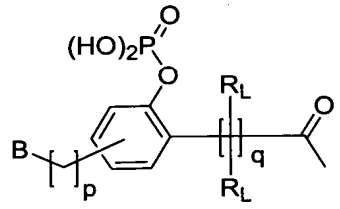


wherein:

B represents said phosphonated group;

n is an integer ≤ 10;

each **p** is independently 0 or an integer ≤ 10;

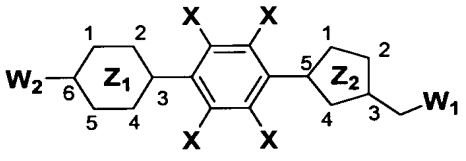
each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl;

q is 2 or 3;

X is CH_2, —CONR$_L$—, —CO—O—CH_2—, or —CO—O—; and

$\mathbf{R_a}$ is C_xH_y where x is an integer of 0 to 20 and y is an integer of 1 to 2x+1.

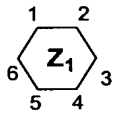
8. The compound of claim 1, wherein **A** has a structure represented by the following Formula (A_1):



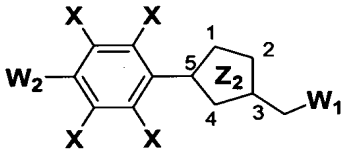
(A_1)

as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

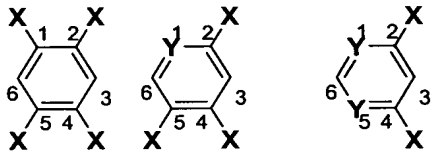
Each of **X** is independently hydrogen or a halogen, preferably a hydrogen or fluorine;



is either absent, in which case A_1 becomes



or is selected from the group consisting of formulae **M1-M3**

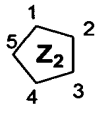


M1 , **M2** and **M3**

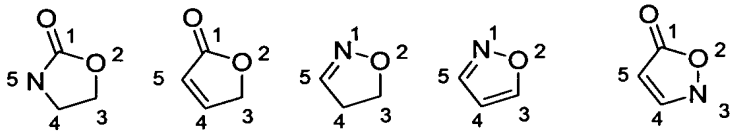
Wherein:

each **X** is defined as above;

each **Y** is independently N or CH



is selected from the group consisting of formulae **M4-M8**

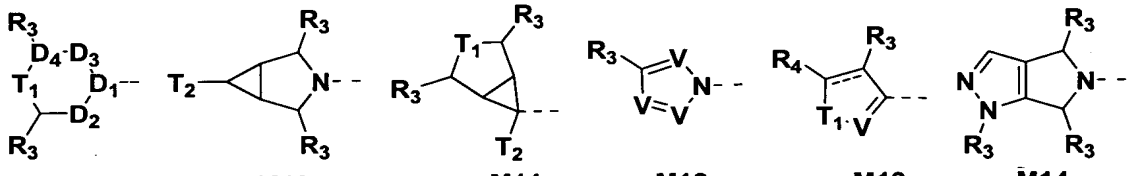


M4 , **M5** , **M6** , **M7** and **M8**

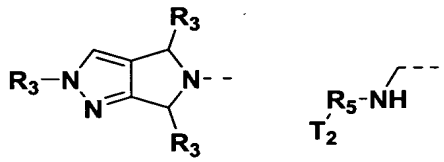
W_1 is hydroxy, halo, amino, azido, (1-4C)alkanesulfonyloxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, $NHS(O)_m$(1-4C)alkyl, $NHCOR_c$, $NHCSR_c$; isoxazol-3-oxy, isothiazol-3-oxy, (1,2,5-thiadiazol)-3-oxy, (1,2,5-oxadiazol)-3-oxy, isoxazol-3-amino, isothiazol-3- amino, (1,2,5-thiadiazol)-3- amino, (1,2,5-oxadiazol)-3-amino, tetrazol-2-yl, tetrazol-1-yl, (1,2,3-triazol)-1-yl, or (4-ethynyl-1,2,3-triazol)-1-yl

wherein: **m** is 0, 1, or 2 and R_c is H, (1-4C)alkyl, (1-4C)dihaloalkyl, (1-4C)alkoxy, methoxymethyl, acetylmethyl, methylamino or dimethylamino;

W_2 is selected from the group consisting of formulae **M9-M16**



M9 , **M10** , **M11** , **M12** , **M13** , **M14** ,



M15 and **M16**

D_1, is independently CH or N and D_2, D_3 and D_4, are each independently CH, CH_2, N, S or O and each ===== represents either a single bond or a double bond;

R_3 are each independently H, CH_3, CN, hydroxyl, bromo, oxo (=O), (1-4C)alkyl, (1-4C)alkylamino, (1-4C)alkoxycarbonyl or CO_2R_d, wherein R_d is H, (1-5C)alkyl, phenyl, or heteroaryl;

T_1 is O, S, SO, SO_2, NH, NR_a, $NCOCH_2OH$, or $NCOR_a$, $C(OH)CH_2N(R_a)_2$, $C(OH)CH_2OR_a$, CH-(tetrazol-2-yl), or CH(tetrazol-1-yl)

wherein each $\mathbf{R_a}$ is independently H, aryl, (1-4C)alkyl, cycloalkyl, heteroaryl, amino, (1-4C)alkylamino, or OR_b, wherein $\mathbf{R_b}$ is (1-6C)alkyl

$\mathbf{T_2}$ is hydroxyl, amino, chloro, fluoro, bromo, $-CO_2H$, cyano, or $-C(O)N(R_d)_2$, wherein each R_d is defined as above.

V is N or CH

$\mathbf{R_4}$ is H or (1-4C) alkyl, $-(CH_2)_x-(CH(OH))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NH_2))-(CH_2)_y-Q$ or $-(CH_2)_x-C(O)-(CH_2)_y-Q$, wherein x and y are independently 0,1 or 2 and Q is $N(R_d)_2$, imidazol-1-yl, 2-methyl-imidazol-1-yl, tetrazol-2-yl, or (1,2,3-triazol)-1-yl, with R_d defined as above.

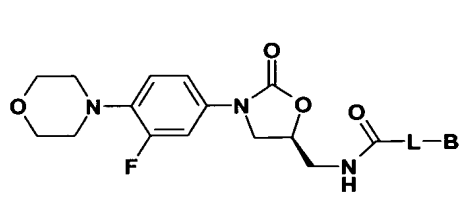
$\mathbf{R_5}$ is one of either $-C_aH_b$, $-(CH_2)_a-(CH(OH))-(CH_2)_c-$, $-(CH_2)_a-(CH(NH_2))-(CH_2)_c-$, $-(CH_2)_a-(CH(OH))-(CH_2)_c-C(O)-$, or $-(CH_2)_a-(CH(NH_2))-(CH_2)_c-C(O)-$, wherein a is an integer ≥ 0 and ≤ 10, b is an integer and ≥ 0 and $\leq 2a$ and c is 0,1 or 2.

9. The compound of claim 1, wherein A is linezolid or a derivative thereof.

10. The compound of claim 1, wherein A is eperezolid or a derivative thereof.

11. The compound of claim 1, wherein A is N-((3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (eperezolid amine) or a derivative thereof.

12. The compound of claim 1, wherein A has a structure selected from the group consisting of: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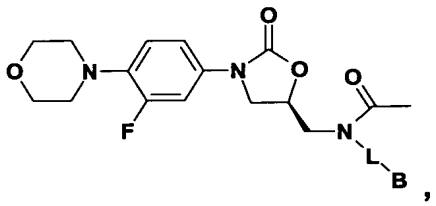
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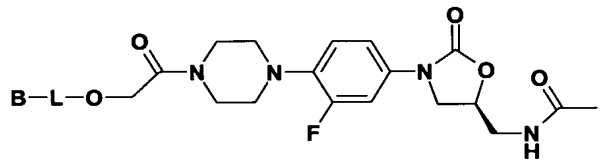
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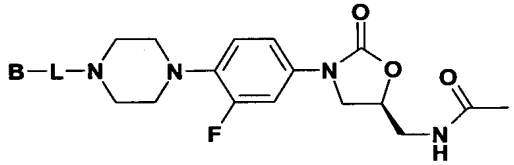
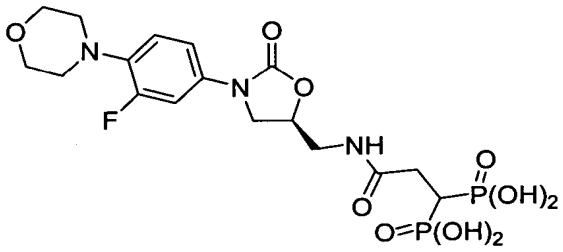


wherein **L** represents said linker or bond, and **B** represents said phosphonated group.

13. The compound of claim 1, wherein said compound is selected from the group consisting of:



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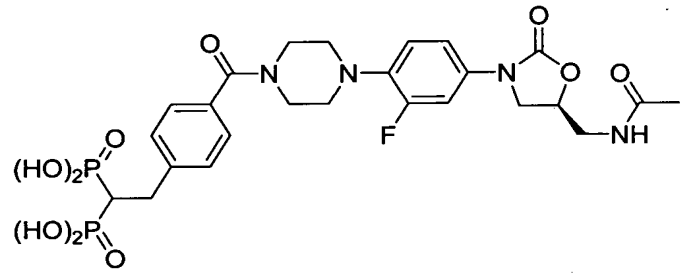

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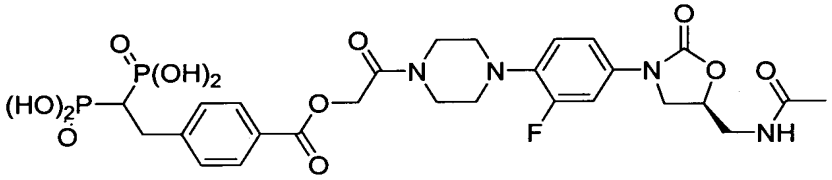

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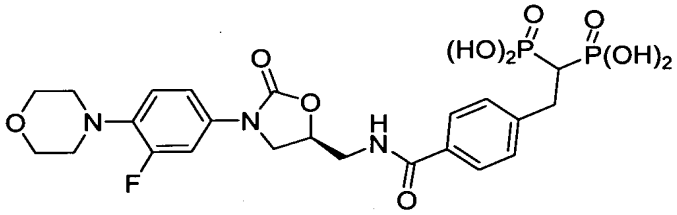

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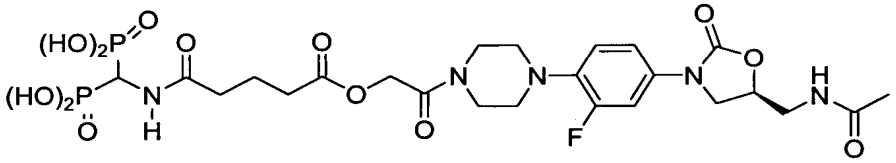

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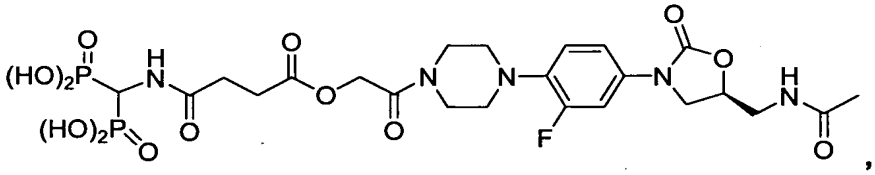

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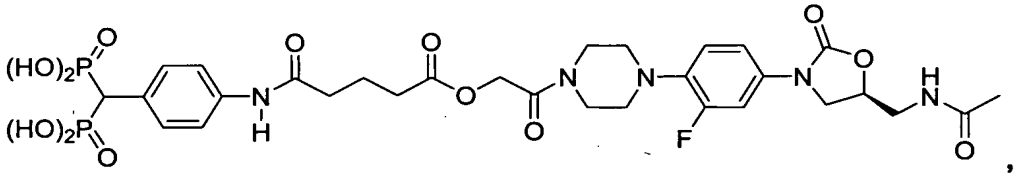

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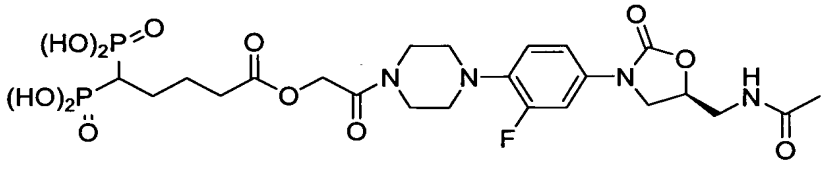

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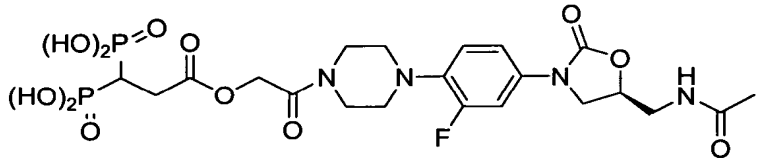

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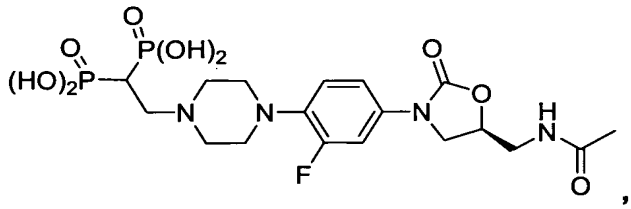

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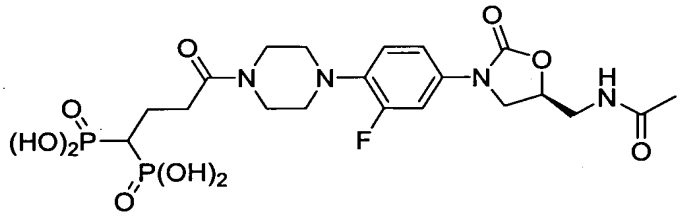

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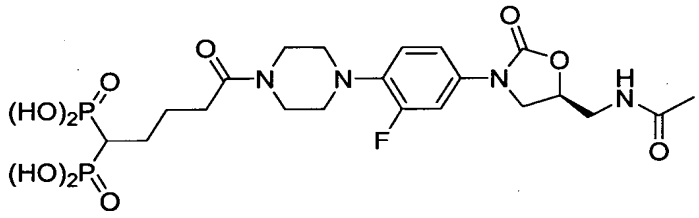

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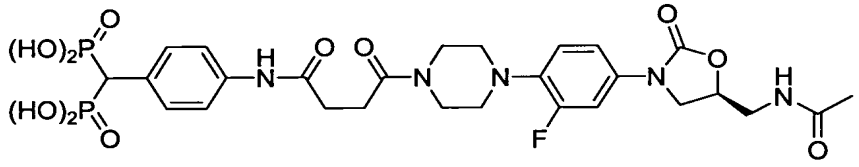

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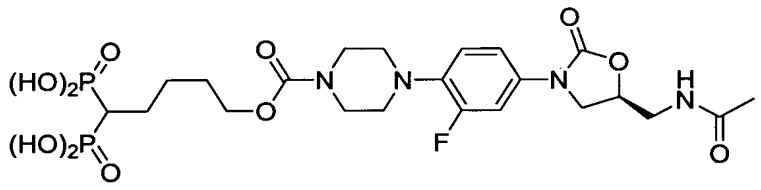

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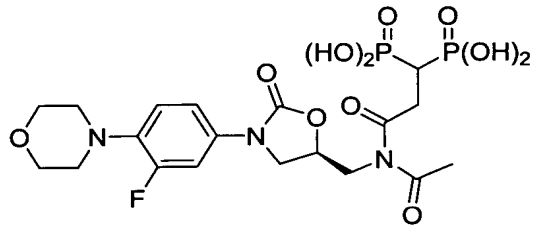

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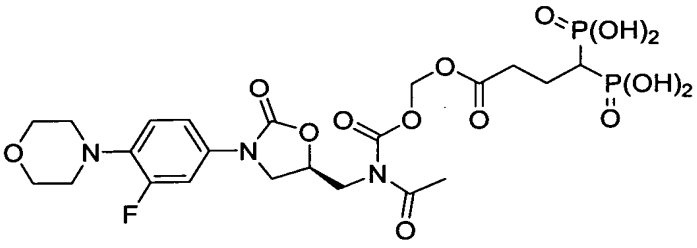
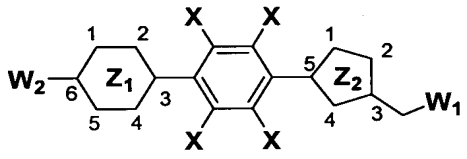


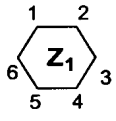
14. The compound of claim 1 represented by the following Formula (II):



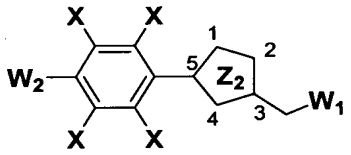
(II)

as well as pharmaceutically acceptable salts, esters and prodrugs thereof, where:

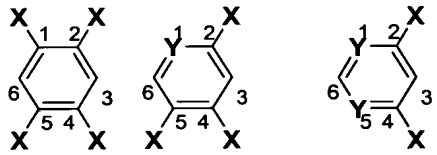
Each of **X** is independently hydrogen or a halogen, preferably a hydrogen or fluorine;



is either absent, in which case II becomes



or is selected from the group consisting of formulae **M1-M3**

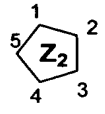


M1 , **M2** and **M3**

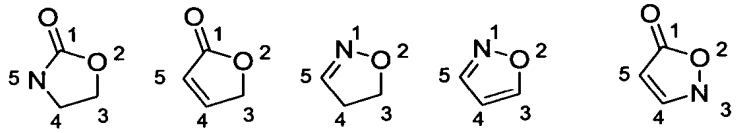
Wherein:

each **X** is defined as above;

each **Y** is independently N or CH



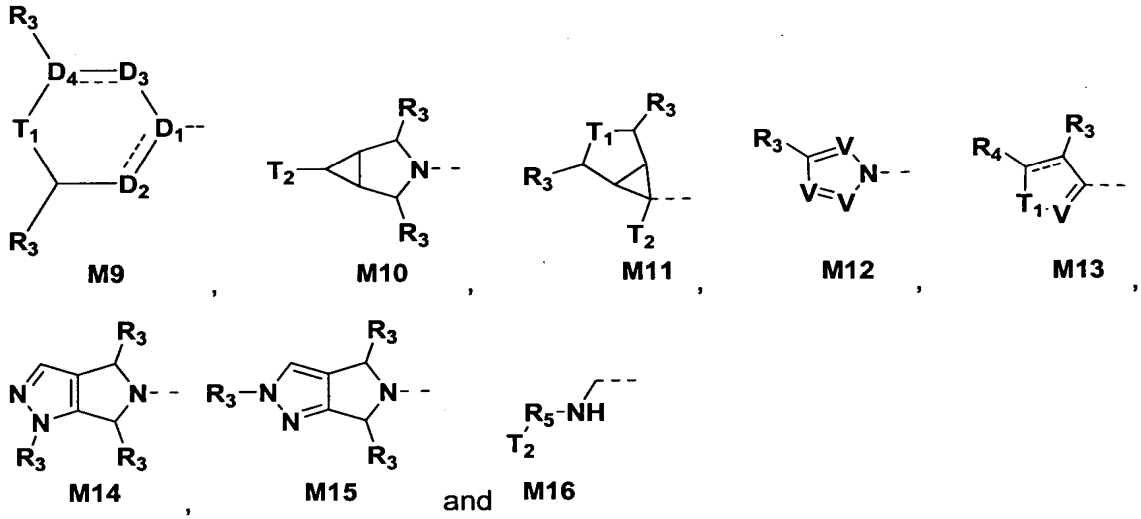
is selected from the group consisting of formulae **M4-M8**



M4 , **M5** , **M6** , **M7** and **M8**

W_1 is hydroxy, halo, amino, azido, (1-4C)alkanesulfonyloxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, $NHS(O)_m$(1-4C)alkyl, $NHCOR_c$ or $NHCSR_c$; isoxazol-3-oxy, isothiazol-3-oxy, (1,2,5-thiadiazol)-3-oxy, (1,2,5-oxadiazol)-3-oxy, isoxazol-3-amino, isothiazol-3- amino, (1,2,5-thiadiazol)-3- amino, (1,2,5-oxadiazol)-3-amino, tetrazol-2-yl, tetrazol-1-yl, (1,2,3-triazol)-1-yl, (4-ethynyl-1,2,3-triazol)-1-yl, $-OL_1$, or $-N(R_c)L_2$ wherein: **m** is 0, 1, or 2; and R_c is H, (1-4C)alkyl, (1-4C)dihaloalkyl, (1-4C)alkoxy, methoxymethyl, acetylmethyl, methylamino or dimethylamino;

W_2 is selected from the group consisting of formulae **M9-M16**



M9 , **M10** , **M11** , **M12** , **M13** , **M14** , **M15** and **M16**

D_1, is independently CH or N and D_2, D_3 and D_4, are each independently CH, CH_2, N, S or O and each ⎓ represents either a single bond or a double bond;

R_3 are each independently H, CH_3, CN, hydroxyl, bromo, oxo (=O), (1-4C)alkyl, (1-4C)alkylamino, (1-4C)alkoxycarbonyl, CO_2R_d, or $-OL_3$ wherein R_d is H, (1-5C)alkyl, phenyl, or heteroaryl;

T_1 is O, S, SO, SO_2, NH, NR_a, $NCOCH_2OH$, $NCOR_a$, $C(OH)CH_2N(R_a)_2$, $C(OH)CH_2OR_a$, CH-(tetrazol-2-yl), CH(tetrazol-1-yl), NL_4, $CHOL_5$, $C(OL_6)CH_2N(R_a)_2$, $C(OH)CH_2N(R_a)L_7$, $C(OL_8)CH_2OR_a$, or $C(OH)CH_2OL_9$

wherein each $\mathbf{R_a}$ is independently H, aryl, (1-4C)alkyl, cycloalkyl, heteroaryl, amino, (1-4C)alkylamino, or OR_b, wherein $\mathbf{R_b}$ is (1-6C)alkyl

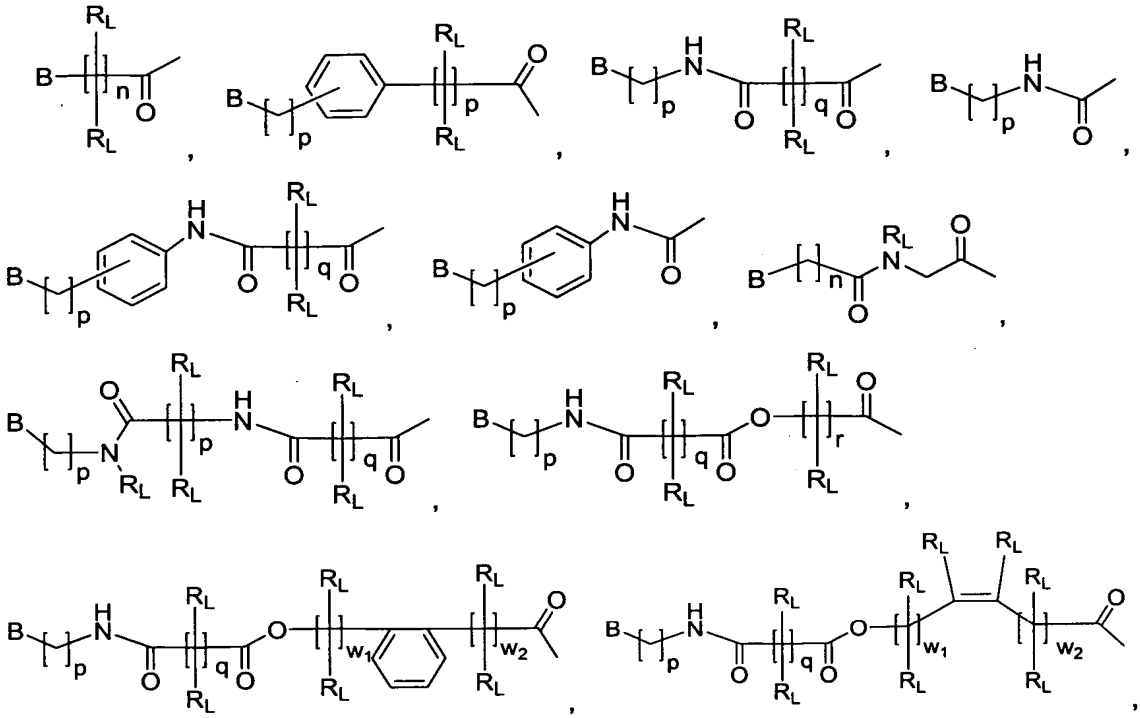
$\mathbf{T_2}$ is hydroxyl, amino, chloro, fluoro, bromo, $-CO_2H$, cyano, $-C(O)N(R_d)_2$, $-OL_{10}$, $-N(R_d)L_{11}$, $-N(L_{12})_2$, $-C(O)N(L_{13})_2$ or $-C(O)N(R_d)(L_{14})$ wherein each R_d is defined as above.

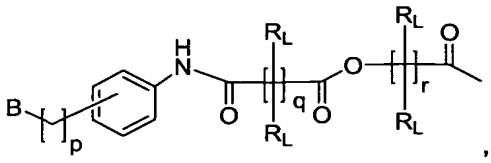
V is N or CH

$\mathbf{R_4}$ is H or (1-4C) alkyl, $-(CH_2)_x-(CH(OH))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NH_2))-(CH_2)_y-Q$, , $-(CH_2)_x-(CH(OL_{15}))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(NHL_{16}))-(CH_2)_y-Q$, $-(CH_2)_x-(CH(N(L_{17})_2))-(CH_2)_y-Q$ or $-(CH_2)_x-C(O)-(CH_2)_y-Q$, wherein x and y are independently 0,1 or 2 and Q is $N(R_d)_2$, $N(R_d)L_{18}$, $N(L_{19})_2$ imidazol-1-yl, 2-methyl-imidazol-1-yl, tetrazol-2-yl or (1,2,3-triazol)-1-yl, with R_d defined as above.

$\mathbf{R_5}$ is one of either $-C_mH_n$, $-(CH_2)_m-(CH(OH))-(CH_2)_b-$, $-(CH_2)_m-(CH(NH_2))-(CH_2)_b-$, $-(CH_2)_m-(CH(OH))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(NH_2))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(OL_{20}))-(CH_2)_b-$, $-(CH_2)_m-(CH(NHL_{21}))-(CH_2)_b-$, $-(CH_2)_m-(CH(N(L_{22})_2))-(CH_2)_b-$, $-(CH_2)_m-(CH(OL_{23}))-(CH_2)_b-C(O)-$, $-(CH_2)_m-(CH(NHL_{24}))-(CH_2)_b-C(O)-$, or $-(CH_2)_m-(CH(N(L_{25})_2))-(CH_2)_b-C(O)-$, wherein m is an integer ≥ 0 and ≤ 10, n is an integer and ≥ 0 and $\leq 2m$ and b is 0,1 or 2.

Each $\mathbf{L_1}$, $\mathbf{L_3}$, $\mathbf{L_5}$, $\mathbf{L_6}$, $\mathbf{L_8}$, $\mathbf{L_9}$, $\mathbf{L_{10}}$, $\mathbf{L_{15}}$, $\mathbf{L_{20}}$, and $\mathbf{L_{23}}$ is a linker independently selected from the group of

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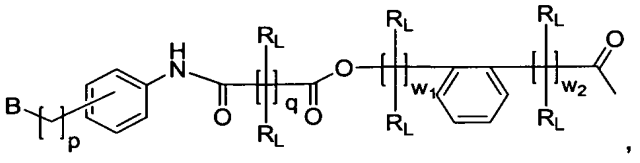
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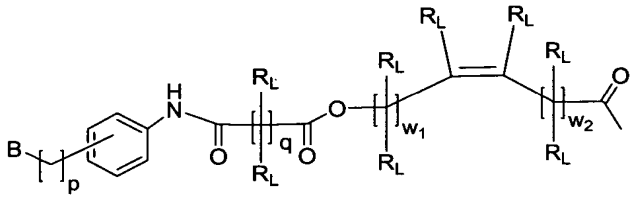
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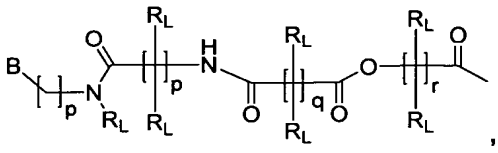
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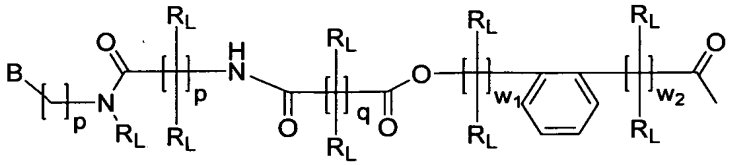
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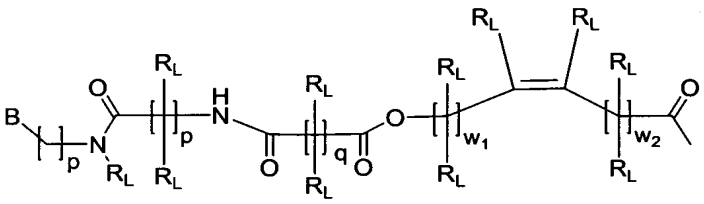


wherein:

B represents said phosphonated group;

each **p** is independently 0 or an integer ≤ 10;

each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl;

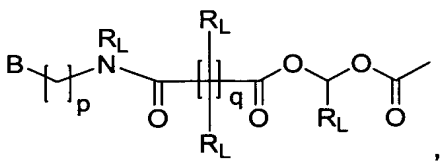
q is 2 or 3;

n is an integer ≤ 10;

r is 1, 2, 3, 4 or 5; and

$\mathbf{w_1}$ and $\mathbf{w_2}$ are each integers ≥ 0 such that their sum ($\mathbf{w_1} + \mathbf{w_2}$) is 1, 2 or 3.

Each $\mathbf{L_2}$, $\mathbf{L_4}$, $\mathbf{L_7}$, $\mathbf{L_{11}}$, $\mathbf{L_{12}}$, $\mathbf{L_{13}}$, $\mathbf{L_{14}}$, $\mathbf{L_{16}}$, $\mathbf{L_{17}}$, $\mathbf{L_{18}}$, $\mathbf{L_{19}}$, $\mathbf{L_{21}}$, $\mathbf{L_{22}}$, $\mathbf{L_{24}}$, and $\mathbf{L_{25}}$ is a linker independently selected from the group of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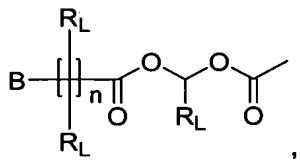
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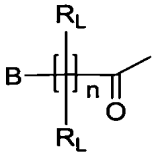
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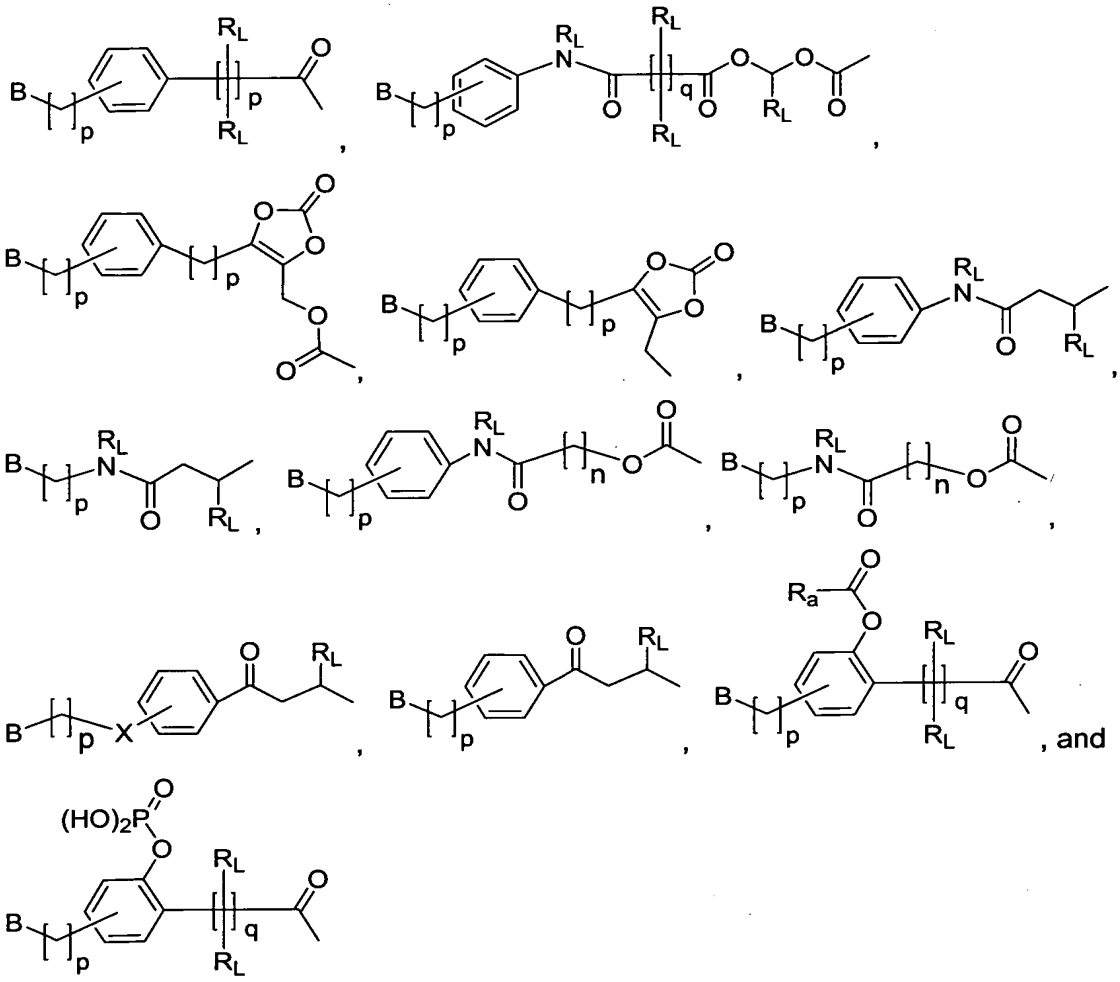


wherein:

B represents said phosphonated group;

n is an integer ≤ 10;

each **p** is independently 0 or an integer ≤ 10;

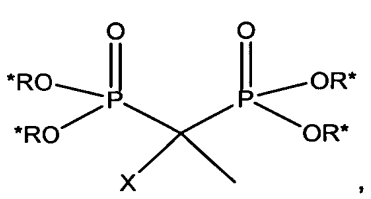
each $\mathbf{R_L}$ is independently selected from the group consisting of H, ethyl and methyl;

q is 2 or 3;

X is CH_2, —CON$\mathbf{R_L}$—, —CO—O—CH_2—, or —CO—O—; and

$\mathbf{R_a}$ is C_xH_y where x is an integer of 0 to 20 and y is an integer of 1 to 2x+1.

B is a phosphonated group selected from the group consisting of:



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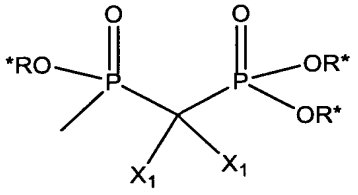

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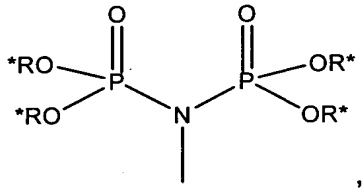

,

wherein:

each **R*** is independently selected from the group consisting of H, lower alkyl, cycloalkyl, aryl and heteroaryl, with the proviso that at least two **R*** are H;

X is H, OH, NH_2, or a halo group;

each $\mathbf{X_1}$ is independently selected from the group consisting of H, OH, NH_2, and a halo group;

with the proviso that at least one of $\mathbf{L_1}$, $\mathbf{L_2}$, $\mathbf{L_3}$, $\mathbf{L_4}$, $\mathbf{L_5}$, $\mathbf{L_6}$, $\mathbf{L_7}$, $\mathbf{L_8}$, $\mathbf{L_9}$, $\mathbf{L_{10}}$, $\mathbf{L_{11}}$, $\mathbf{L_{12}}$, $\mathbf{L_{13}}$, $\mathbf{L_{14}}$, $\mathbf{L_{15}}$, $\mathbf{L_{16}}$, $\mathbf{L_{17}}$, $\mathbf{L_{18}}$, $\mathbf{L_{19}}$, $\mathbf{L_{20}}$, $\mathbf{L_{21}}$, $\mathbf{L_{22}}$, $\mathbf{L_{23}}$, $\mathbf{L_{24}}$ and $\mathbf{L_{25}}$ is present.

15. A composition useful in treating or preventing a bone infection comprising:

(a) effective amount of a compound represented by the general Formula (I) or Formula (II) as defined in any one of claims 1 to 13; and

(b) a pharmaceutically acceptable carrier or excipient.

16. A method for treating or preventing a bacterial infection in a subject, comprising administering to a subject a pharmaceutically effective amount of a compound as defined in any one of claims 1 to 13, 15 to 18, or of a pharmaceutically effective amount of a composition as defined in claim 14.

17. A method of prophylaxis for a bacterial infection in a subject, comprising administering to a subject in need of such prophylaxis a prophylactically effective amount of a pharmaceutical composition according to claim 14.

18. The methods of claims 16 and 17 wherein said subject is a human.

19. The method of claim 16, further comprising administering an antibiotic concurrent with administration of said pharmaceutical composition.

20. The method of claim 19, wherein said antibiotic is selected from the group consisting of tetracycline, a tetracycline derived antibacterial agent, glycylcycline, a glycylcycline derived antibacterial agent, minocycline, a minocycline derived antibacterial agent, an oxazolidinone antibacterial agent, an aminoglycoside antibacterial agent, a quinolone antibacterial agent, vancomycin, a vancomycin derived antibacterial agent, a teicoplanin, a teicoplanin derived antibacterial agent, eremomycin, an eremomycin derived antibacterial agent, chloroeremomycin, a chloroeremomycin derived antibacterial agent, daptomycin, a daptomycin derived antibacterial agent, Rifamycin, a Rifamycin derived antibacterial agent, Rifampin, a Rifampin derived antibacterial agent, Rifalazil, a Rifalazil derived antibacterial agent, Rifabutin, a Rifabutin derived antibacterial agent, Rifapentin, a Rifapentin derived antibacterial agent, Rifaximin and a Rifaximin derived antibacterial agent.

21. A method of inducing accumulation of an oxazolidinone antimicrobial molecule in bones of a mammal, comprising:

- providing a phosphonated derivative of an oxazolidinone antimicrobial molecule, wherein said phosphonated derivative comprises a phosphonated group having a high affinity to osseous tissues; and
- administering said phosphonated derivative to a mammal.

whereby said phosphonated derivative binds osseous tissues and accumulates in bones of said mammal in amounts greater than amounts of a non-phosphonated equivalent of said oxazolidinone antimicrobial molecule.

22. A method for prolonging the presence of an oxazolidinone antimicrobial molecule in bones of a mammal, comprising:

- providing a phosphonated derivative of an oxazolidinone antimicrobial molecule, wherein said phosphonated derivative comprises a phosphonated group having a high affinity to osseous tissues, and wherein said phosphonated group is coupled to said oxazolidinone antimicrobial molecule through a cleavable linker; and
- administering said phosphonated derivative to a mammal.

whereby said phosphonated derivative binds osseous tissues and accumulates in bones of said mammal, and whereby said linker is cleaved gradually within the bones thereby releasing said oxazolidinone antimicrobial molecule and prolonging the presence thereof in said bones.

23. The method of claim 21 or 22, wherein said phosphonated derivative is represented by the general Formula (I) or Formula (II) as defined in any one of claims 1 to 14.

24. All novel compounds, processes, methods and uses substantially as hereinbefore described with particular references to the Examples.

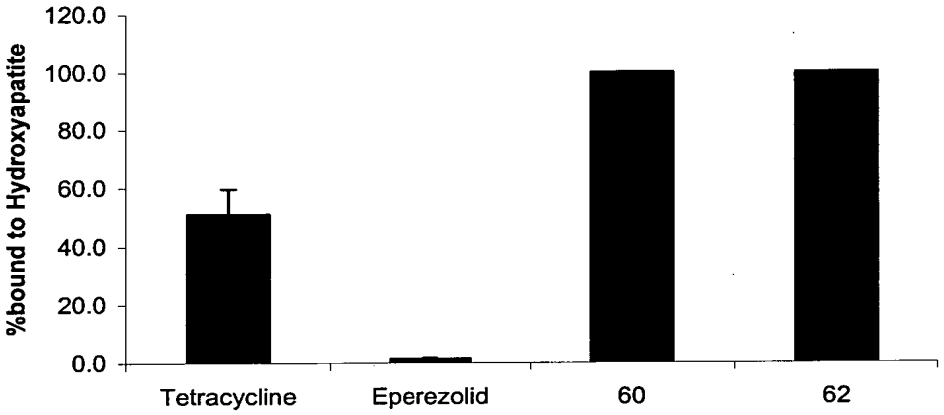

FIGURE 1

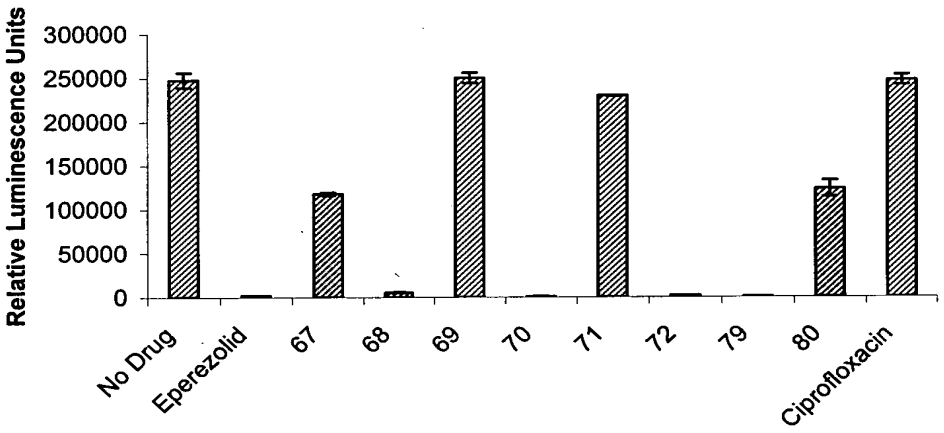

FIGURE 2

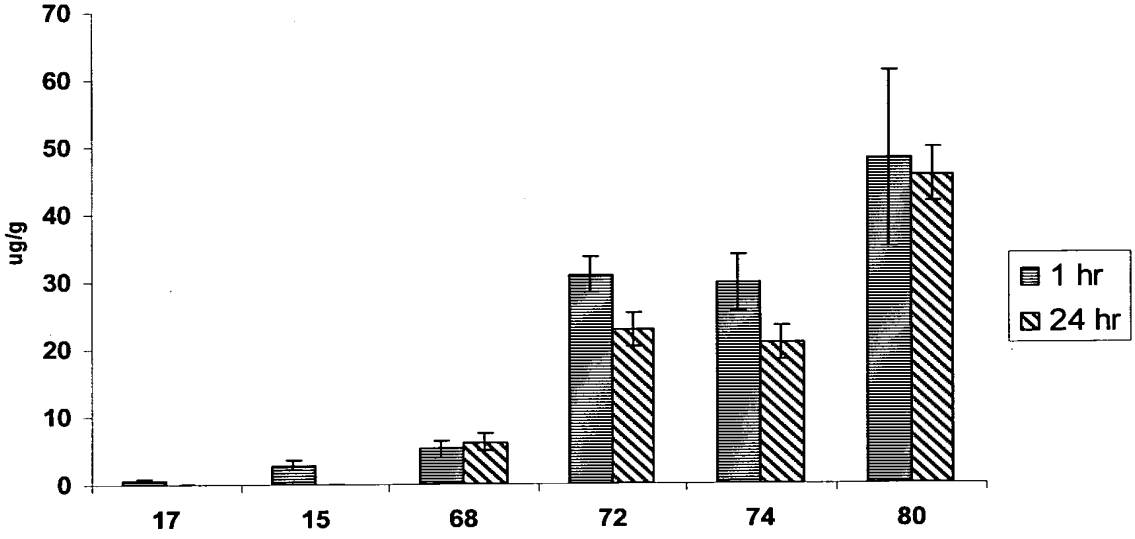

FIGURE 3

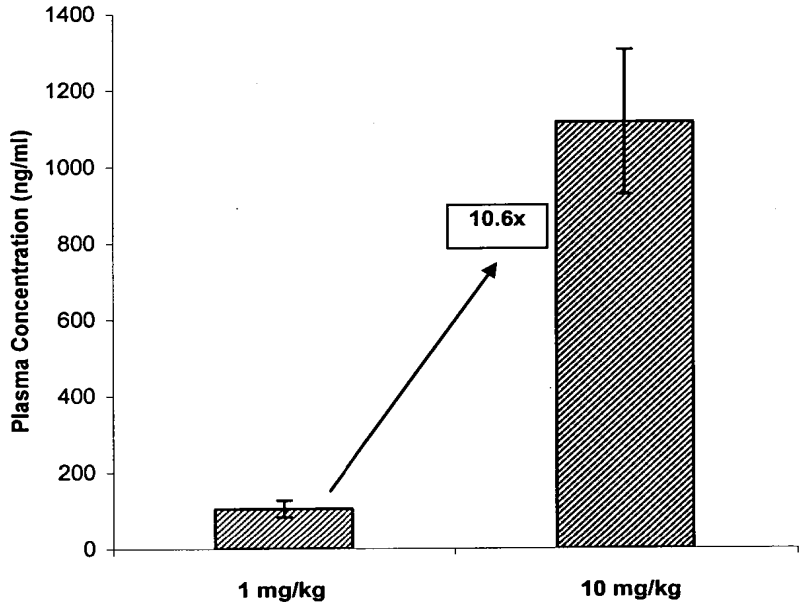

FIGURE 4

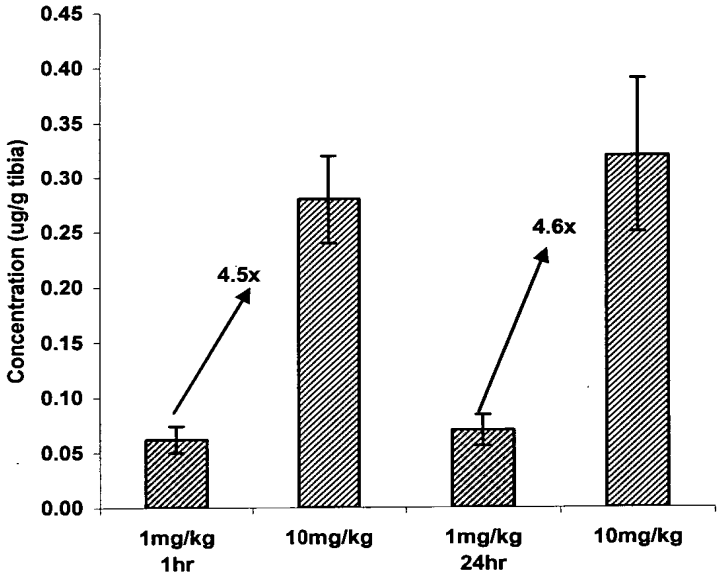

FIGURE 5A

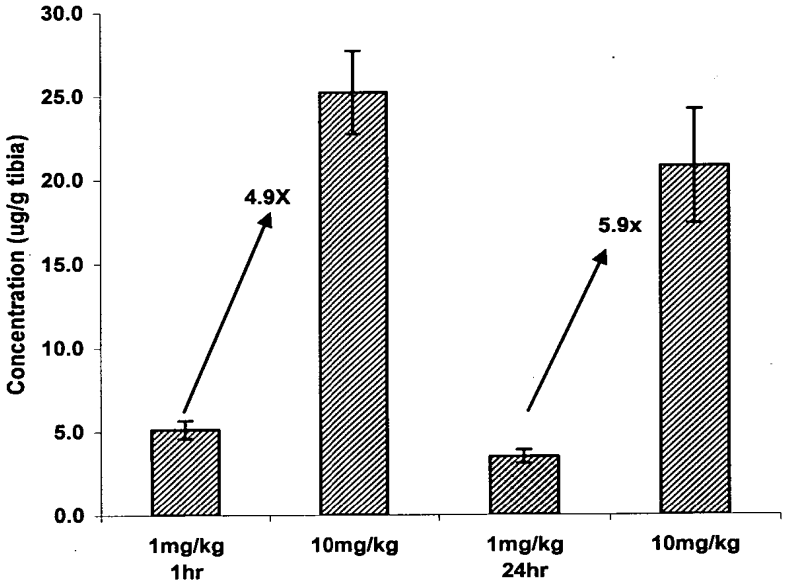

FIGURE 5B

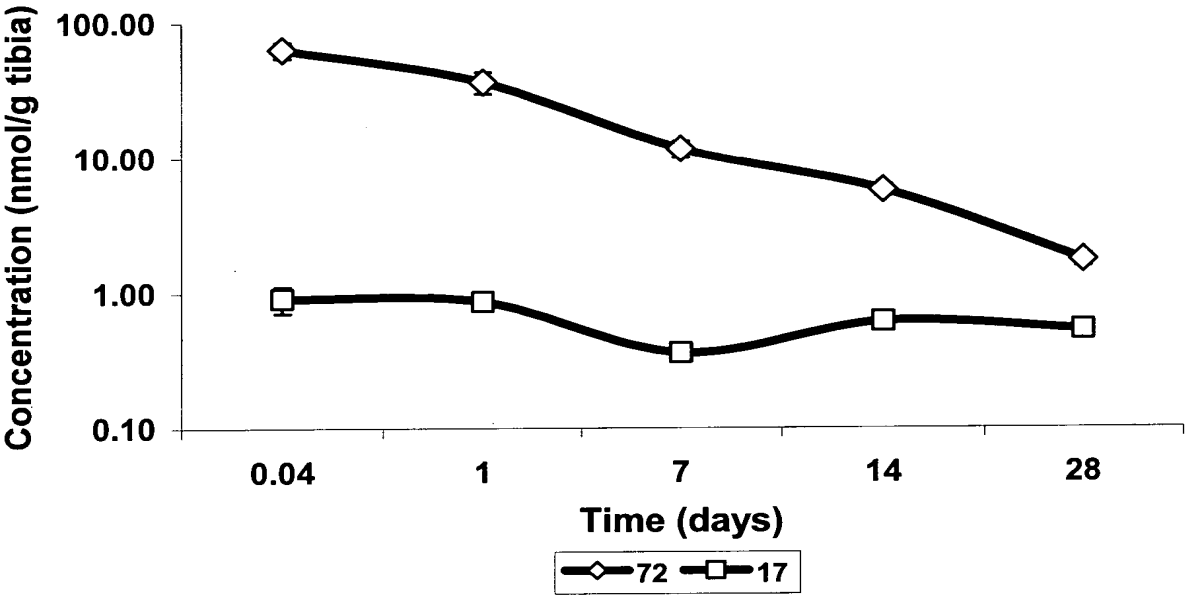
Concentration (nmol/g tibia)
100.00
10.00
1.00
0.10
0.04
1
7
14
28
Time (days)
72
17

FIGURE 6